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(54) **Pharmaceutically active compounds.**

(57) The disclosed invention is compounds represented by the formula

Z-X-Q-Y-W'-Y-Q-X-Z II

and pharmaceutically acceptable acid addition, basic addition salts and quarternary amine salts thereof and pharmaceutically acceptable solvates thereof, wherein

each Z is independently tetiary butyl, phenyl, naphthyl or adamantyl; substituted phenyl wherein the substituents are one or more of halogen, lower alkoxy, phenoxy, nitrile, nitro, phenylsulfonyl, loweralkylsulfonyl, oxazol-2-yl, lower alkanoyl, benzoyl, lower alkoxycarbonyl, lower alkyl, lower alkylthio, phenyl, phenylaminothiocarbonyl, or lower alkylaminothiocarbonyl; 4 or 6 membered unsubstituted or substituted heterocyclic ring containing at least one nitrogen with the remaining ring members being at least one carbon, and optionally sulfur or oxygen, wherein the substituents are one or more of carboxyl, hydroxymethyl, lower alkyl, loweralkylcarbonyl or aryl lower alkyl;

X and Y are each independently a bond, -O-, -S-, -SO_2-,

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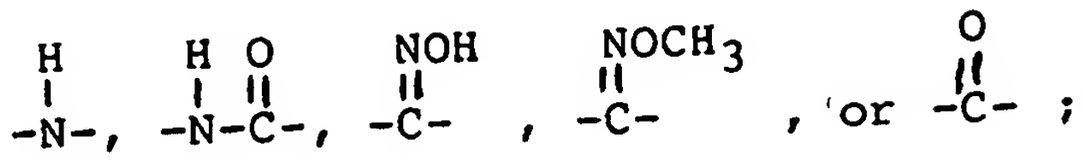


each Q is independently a divalent substituted or unsubstituted straight or branched chain lower alkanediyl, lower alkanediyl-cycloalkanediyl-lower alkanediyl, lower alkenediyl, lower alkynediyl, phenylene, dihydrofurandiyl, tetrahydrofurandiyl, tètrahydropyrandiyl,, or loweralkanediyl-tetrahydrofurandiyl-loweralkanediyl, wherein the substituents are one or more of hydroxy, epoxy, fluorine, chlorine, azide, or amino;

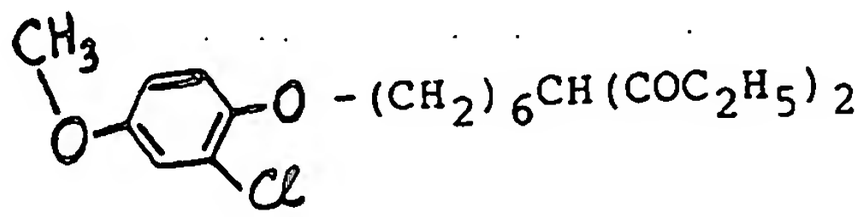
W is a monovalent substituted or unsubstituted aryl group or a heterocyclic single or fused ring containing from 4 to 10 ring atoms, at least one hetero atom of which is a nitrogen atom and the remaining ring atoms being at least one carbon and optionally sulfur or oxygen, wherein the substituents are one or more of hydroxy, oxo, amino, carbamoyl, carboxyl, nitrile, nitro, lower alkoxy carbonyl, halogen, sulfamyl, lower alkyl, lower alkylthio, lower alkoxy, hydroxyloweralkyl, lower alkoxycarbonylloweralkyl, amino loweralkyl, carboxyloweralkyl, guanidino, thioureido, lower alkylsulfonyl-amino, aminocarbonylloweralkyl, allyloxycarbonylmethyl or carbamoyloxyloweralkyl; with the proviso that W cannot be substituted or unsubstituted isoxazolyl, and

W' is divalent W.

The compounds have antiviral activity, antiinflammatory activity and are PAF inhibitors.

This invention relates to compounds with pharmaceutical activity, i.e. antiviral, antiinflammatory and platelet activating factor inhibition, their pharmaceutically acceptable salts and solvates and pharmaceutical compositions containing the active compounds.

Arildone, a compound represented by the formula



is active in vitro against herpes virus and polio virus, but is only marginally active against rhinoviruses. Diana et al., J. Med. Chem. 28, 748 (1985) prepared some alkyl-substituted isoxazole analogs of arildone in an attempt to prepare compounds with broad spectrum activity against picornaviruses. Some of the compounds were active against both rhinovirus type 2 and poliovirus type 2. However, there is no indication that any of the Diana et al. compounds have activity as antiinflammatories or as platelet activating factor inhibitors. Many of the compounds of this invention possess such activity.

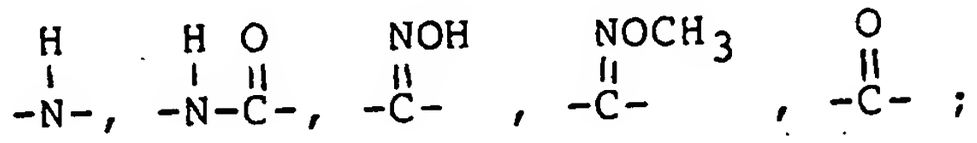
The compounds of this invention are represented by the following structural formulas I and II

Z-X-Q-Y-W I

Z-X-Q-Y-W'-Y-Q-X-Z II

pharmaceutically acceptable acid addition, basic addition, and quaternary amine salts thereof and pharmaceutically acceptable solvates thereof, wherein each Z is independently tertiary butyl, phenyl, naphthyl or adamantanyl; substituted phenyl, wherein the substituents are one or more of halogen, lower alkoxy, phenoxy, nitrile, nitro, phenylsulfonyl, loweralkylsulfonyl, oxazol-2-yl, lower alkanoyl, benzoyl, lower alkoxycarbonyl, lower alkyl, phenyl, lower alkylthio, phenylaminothiocarbonyl, or lower alkylaminothiocarbonyl; 4 to 6 membered unsubstituted or substituted heterocyclic ring containing at least one nitrogen in the ring with the remaining members of the ring being at least one carbon, and optionally sulfur or oxygen wherein the substituents are one or more of -COOH, $-CH_2OH$, lower alkyl, loweralkylcarbonyl, or aryl lower alkyl;

X and Y are each independently a bond, -O-, -S-, $-SO_2-$,



each Q is independently a divalent substituted or unsubstituted, straight or branched chain lower alkanediyl, loweralkanediyl-cycloalkanediyl-loweralkanediyl, lower alkenediyl, lower alkynediyl, phenylene, dihydrofurandiyl, tetrahydrofurandiyl, tetrahydropyrandiyl, loweralkanediyl-tetrahydrofurandiyl-loweralkanediyl wherein the substituents are one or more of hydroxy, epoxy, fluorine, chlorine, azide, or amino;

W is a monovalent substituted or unsubstituted aryl group or a heterocyclic single or fused ring containing from 4 to 10 ring atoms, at least one hetero atom of which is a nitrogen atom and the remaining ring atoms being at least one carbon and optionally sulfur or oxygen, wherein the substituents are one or more of hydroxy, oxo, amino, carbamoyl, carboxyl, nitrile, nitro, lower alkyl, loweralkoxycarbonyl, halogen, sulfamyl, loweralkoxycarbonylloweralkyl, loweralkythio, lower alxoxy, hydroxy loweralkyl, amino loweralkyl, carboxy loweralkyl, guanidino, thioureido, lower alkyl sulfonylamino, aminocarbonylloweralkyl, allyloxycarbonyl-methyl or carbamoyloxyloweralkyl, with the proviso that W cannot be substituted or unsubstituted isoxazolyl,

W' is divalent W.

Compounds of formula I form the subject of European patent application number 87310807.0 of which the present application is a divisional application.

The invention also includes pharmaceutical compositions containing pharmaceutically effective amounts of a compound of formula I or formula II as well as method of treating virus infections, inflammation and inhibiting platelet activating factor using the appropriate pharmaceutical compositions.

As used herein "lower alkyl" alone or in combined form, e.g. "lower alkoxy" or "loweralkanediyl", means straight or branched chain alkyl groups of from 1 to 10 carbon atoms, e.g. methyl, ethyl, propyl,

isopropyl, butyl, t-butyl, pentyl, neopentyl, hexyl and the like.

The heterocyclics at Z and W are monovalently bonded to X and Y respectively by a hetero atom, preferably nitrogen, or by a carbon atom. The heterocyclics at W' preferably have two nitrogens, each of which is bonded to a separate -Y-Q-X-Z moiety.

Heterocyclic groups within the scope of this invention for Z are, for example, imidazolyl (such as imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, and imidazol-5-yl), dihydrothiazolyl (such as 4, 5-dihydrothiazol-2-yl), tetrazol (such as tetrazol-5-yl, tetrazol-1-yl, and tetrazol-2-yl), pyridinyl (such as pyridin-2-yl), triazolyl (such as 1, 2, 4-triazol-1-yl), tetrahydro-pyrimidinyl (such as 1, 2, 3, 4-tetrahydro-pyrimidin-1-yl), dihydro-oxazolyl (such as 4, 5-dihydro-oxazol-2-yl), pyrrolidinyl (such as pyrrolidin-1-yl), pyrazolyl (such as pyrazol-1-yl and pyrazol-2-yl), morpholinyl, and azetidinyl. All possible attachment positions of the above heterocyclic groups are within the scope of this invention.

Heterocyclic groups within the scope of this invention for W are, for example, all those listed above for Z and, in addition, fused ring compounds, for example benzamidazolyl (such as benzamidazol-1-yl and benzamidazol-2-yl), naphthyridinyl (such as naphthyridin-1-yl), purine (such as purine-9-yl and purine-7-yl), and quinolinyl.

Heterocyclic groups within the scope of this invention for W' are all those listed above for Z and W, but being divalent. For example, if W' were tetrahydro-pyrimidinyl, it could be 1, 2, 3, 4-tetrahydro-pyrimidin-1, 3-diyl. W' as a benzamidazolyl group could be, for example benzamidazol-1,3-diyl. In other words, to obtain a possible W' group from the groups listed for Z and W, the "yl" suffix in the Z and W radical is replaced by "diyl".

"Aryl" as used herein refers to phenyl and naphthyl.

"Halogen" as used herein means chlorine, fluorine, bromine or iodine with chlorine or fluorine preferred.

"Cycloalkane", alone or in combined form, means a 4, 5, 6 or 7 membered saturated carbocyclic ring.

"Lower alkene", alone or in combined form, means a 2 to 10 carbon branched or straight chain alkene group.

"Lower alkyne", alone or in combined form, means a 2-10 carbon branched or straight chain alkyne group.

"Pharmaceutically acceptable salts" as used herein means acid addition salts formed from mineral acids such as hydrochloric, hydrobromic, phosphoric or sulfuric acids, or formed from organic carboxylic or sulfonic acids such as trifluoroacetic, para-toluene, sulfonic, maleic, acetic, citric, oxalic, succinic, benzoic, tartaric, fumaric, mandelic, ascorbic and malic acids, or quaternary salts prepared from such organic halides as methyl iodide, ethyl iodide, benzyl chloride and the like, although all pharmaceutically acceptable quaternary salts are contemplated. Basic addition salts are also within the scope of this invention.

The above salts are made by conventional means in the art, e.g. reaction of the compound with the appropriate acid, organic halide, or base.

The preferred salt is the hydrochloride salt.

"Hydroxy protecting group" as used herein means any known hydroxy protecting group which is removed by conventional reactions which do not adversely affect the compounds produced. Typical suitable hydroxy protecting groups are t-butyldimethylsilyl (TBDMS) or tetrahydro-pyranyl.

The compounds of this invention have been found to be active against ether-resistant RNA viruses, i.e. picornaviruses which includes enteroviruses and rhinoviruses. The enteroviruses include poliovirus, coxsackieviruses and echoviruses. Rhinoviruses include those viruses associated with the common cold and certain other respiratory ailments. Over one hundred serotypes are identified. Although the compounds of this invention are not active against all the rhinoviruses, they are active against a large number of them including rhinovirus 2. The compounds of this invention are also active against the enteroviruses such as poliovirus 2, coxsackieviruses A and B3, ECHO and hepatitis A.

In addition, the compounds of this invention are active against certain DNA viruses such as herpesvirus and cytomegalovirus. Thus, they showed activity when tested in in vitro activity assays, i.e. plaque reduction assays which measure the ability of synthetic compounds to neutralize virus infectivity, e.g. picornavirus infectivity. In tests against coxsackievirus 3, the IC_{50} values of the tested compounds of this invention varied from about 0.7 microgram/ml to about 1.4 microgram/ml. The IC_{50} value in all antiviral tests is the concentration of test compound in micrograms per milliliter which results in a 50% decrease in plaque forming units compared to a non-treated control.

In a modified standard test, i.e. wherein the virus and test compound are mixed and incubated prior to overlaying with an agar medium, active compounds of this invention had IC_{50}s of from about 6.0 to about 37.3 against poliovirus 2, about 8.5 to about 39.5 against human rhinovirus 14 and about 2.4 to 5.0 against cosackievirus B3.

The standard test involves overlaying HeLa cells with agar medium containing measured concentrations of the test compound following virus absorption, then incubating for 72 hours. The resulting plaques are stained, visualized and measured to determine virus growth inhibition as evidenced by plaque reduction when compared to a control.

The modified standard test is considered more sensitive because of its ability to discriminate more clearly the virus growth neutralizing effects between compounds whose IC_{50}s are very close according to the standard test.

Of the antiviral compounds within the scope of formulas I and II, those which form water soluble acid addition salts are orally absorbable, show good tissue levels and serum stability.

The preferred antiviral compounds of this invention are those represented by the following formula III

$$Z^1\text{-}X^1\text{-}Q^1\text{-}W^1 \qquad III$$

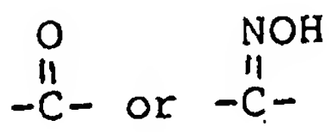
and pharmaceutically acceptable acid addition salts thereof,

wherein

Q^1 is lower alkanediyl of 5, 6 or 7 carbons; lower alkynediyl of 6, 7 or 8 carbon atoms; and all possible isomers of methylcyclohexylmethyl,

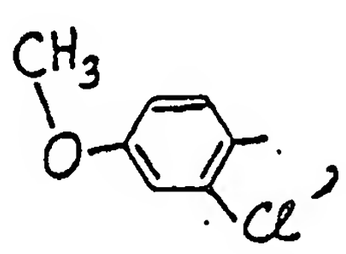
W^1 is unsubstituted or substituted imidazo-1-yl, purin-9-yl or imidazo-2-yl, wherein said substituents are one or more of loweralkyl, hydroxy loweralkyl, nitro, lower alkoxycarbonyl, carboxymethyl, aminocarbonyl-methyl;

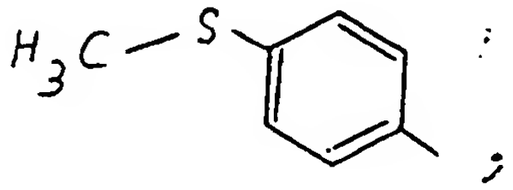
X^1 is -O-,



and

Z^1 is





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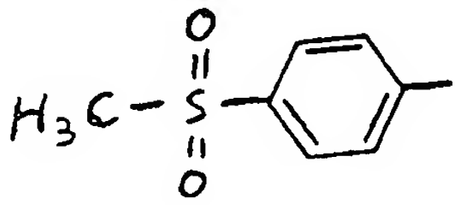


The preferred acid addition salt is the hydrochloride.

Certain compounds of this invention have been found to display activity in animal models of inflammation, Thus, in a reverse passive Arthus reaction in rats, the compounds were orally active when administered at dosages of from 25 to 100 mg/kg and in the adjuvant induced arthritis test in rats were orally active.

The reverse passive Arthus test evaluates test compounds for activity against an immune complex, cell-mediated inflammatory reaction. In the performance of the test, rats previously fasted for 24 hours are dosed with the test compound, then after one hour are lightly anesthesized and injected (iv) with 1.0 mg bovine serum albumin (BSA) in 0.1 ml sterile saline. Then the rats are injected intrapleurally with 0.1 ml sterile saline containing 100 micrograms of antibody protein to bovine serum albumin.

Four hours after challenge, the rats are sacrificed and pleural cavity transudate is removed and the volume recorded. The pleural cavity is then washed with 3 ml of cold saline and the wash is removed and added to the original transudate. After being treated with an anticlot agent or EDTA, the transudate is cooled

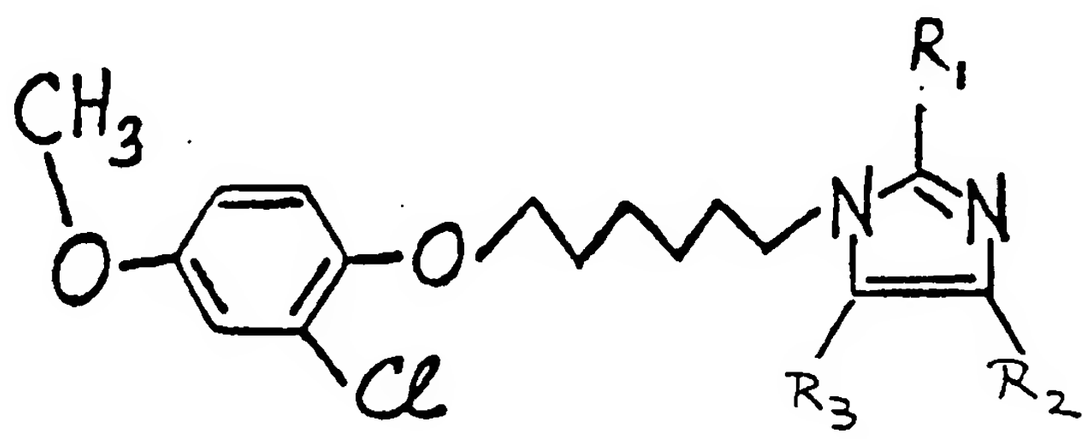
on ice and the volumes of the test transudate and control transudate are adjusted to 5.5 ml with saline and their white blood cell counts are determined on a ZI Coulter Counter. The differences between transudate volume (a measure of edema) and total white blood cell counts (a measure of neutrophil accumulation) between the controls and drug treated groups is a measure of the drugs antiinflammatory activity. These effects are stated as a percent inhibition or reduction in neutrophil count and transudate volume.

The adjuvant induced arthritis test in rats evaluates the effect of a drug on an immune mediated model of chronic inflammation. In the performance of the test, animals (rats) are dosed orally with drugs at a volume of 1 ml per 100 grams of body weight. The drug concentration is varied for different test dosages. The rats are dosed with the test compound one hour prior to sensitization with an adjuvant. The adjuvant used in this test model is heat killed mixed M. tuberculosis homogenized in paraffin oil. Controls are given the methylcellulose vehicle alone.

The adjuvant is injected into the subplantar region of the left hind paw, immediately thereafter the volumes of the left and right hind paws are measured with a plethysmograph. Injected paw volumes are measured after 24 hours and then 21 days later. The contralateral hind paw is only measured 21 days later. The differences in paw volumes between the first and last measurements are related to the degree of inflammation. Antiinflammatory drugs reduce these differences.

The compounds of this invention which exhibit antiinflammatory activity are those with an imidazo-1-yl or lower alkyl substituted imidazo-1-yl at the W position of formula I.

Preferred antiinflammatory compounds of this invention are represented by the following compound IV



IV

and pharmaceutically acceptable acid addition salts thereof, wherein

R_1, R_2 and R_3 are each independently hydrogen hydroxyloweralkyl or lower alkyl, with the proviso that when one of R_2 and R_3 is lower alkyl, the other is hydrogen.

Certain of the compounds of this invention have been found to display platelet-activating factor (PAF) antagonism. PAF has been shown to be involved in the pathophysiology of various allergic and inflammatory diseases. It is an important mediator of such processes as platelet aggregation, smooth muscle contraction, especially lung tissue, vascular permeability and neutrophil activation. Furthermore, recent evidence implicates PAF as the underlying factor involved in airway hyperreactivity. As such, PAF is implicated in diseases such as asthma (bronchoconstriction and pulmonary edema) and inflammation.

Antagonists or inhibitors of PAF, such as the compounds of this invention, would therefore be of use whenever PAF is a factor in the disease or disorder. This includes allergic diseases such as asthma, adult respiratory distress syndrome and urticaria, and inflammatory diseases such as rheumatoid arthritis and osteoarthritis.

In the in vivo PAF Induced Bronchiospasm in Guinea Pigs, compounds of this invention exhibit IC_{50} values of from about 3 to about 60 mg per kg. In the in vitro PAF Antagonism Assay, compounds of this invention show an inhibition of PAF activity from about 20 to 100% at varying concentrations.

The PAF Induced Bronchiospasm in Guinea Pigs assay is conducted as follows:

Non-sensitized guinea pigs were fasted overnight, and the following morning were anesthetized with 0.9 ml/kg i.p. of dialurethane (0.1 gm/ml of diallylbarbituric acid, 0.4 gm/ml of ethylurea and 0.4 gm/ml of methane). The trachea was cannulated and the animals were ventilated by a Harvard rodent respirator at 55 strokes/min with a stroke volume of 4 ml. A side arm to the tracheal cannula was connected to a Harvard pressure transducer to obtain a continuous measure of intratracheal pressure, which was measured on a Harvard polygraph. The jugular vein was cannulated for the adminstration of compounds. The animals were challenged i.v. with PAF (0.4 µg/kg in isotonic saline containing 0.25% BSA) and the peak increase in inflation pressure that occurred within 5 min. after challenge was recorded. Test compounds were administered either orally (2 hours prior to PAF as a suspension in 0.4% methyl cellulose vehicle) or intravenously (10 minutes prior to PAF as a solution in DMSO).

The effect of compounds on the bronchoispasm is expressed as a percent inhibition of the peak increase in intratracheal pressure compared to the peak increase in the control group. The IC_{50} is the dosage in mg/kg required to obtain a 50% inhibition.

The in vitro PAF Antagonism Assay as conducted as follows:

Platelet-activating factor (PAF) causes aggregation of platelets in a receptor-mediated mechanism. Therefore, PAF-induced platelet aggregation provides a simple and convenient assay to screen compounds for PAF antagonism.

Preparation of platelet-rich plasma (PRP)

Human blood (50 ml) is collected from healthy male donors in an anticoagulant solution (5 ml) containing sodium citrate (3.8%) and dextrose (2%). Blood is centrifuged at 110 X g for 15 min. and the supernatant (PRP) carefully transferred into a polypropylene tube. Platelet-poor-plasma (PPP) is prepared by centrifuging PRP at 12,000 X g for 2 min. (Beckman Microfuge B). PRP is used within 3 hours of drawing the blood.

Platelet Aggregation Assay

When an aggregating agent such as PAF is added to PRP, platelets aggregate. An aggregometer quantifies this aggregation by measuring and comparing light (infrared) transmission through PPP and PRP. The aggregation assays performed on the compounds of this invention are performed using a dual-channel aggregometer (Model 440, Chrono-Log Corp., Havertown, PA). PRP (0.45 ml) in aggregometer curettes is continually stirred (37 °C). Solutions of test compounds or vehicle are added to the PRP, and after incubation for 2 min., 10-15 µl aliquots of PAF solution are added to achieve a final concentration of 1-5 X 10^{-8} M. Incubations are continued until the increase in light transmission reaches a maximum (usually 2 min.). Values for inhibition are calculated by comparing maximal aggregation obtained in the absence and the presence of the test compound and expressed as percent inhibition. For each experiment, a standard PAF antagonist such as alprazolam is used as a positive internal control.

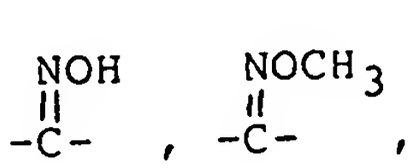
Preferred PAF antagonist compounds of this invention are represented by the following formula V:

$$Z^2\text{-}X^2\text{-}Q^2\text{-}Y^2\text{-}W^2 \qquad V$$

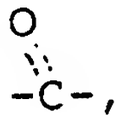
pharmaceutically acceptable acid addition salts or quaternary amine salts thereof, wherein

Z^2 is phenyl; substituted phenyl wherein the substituents are independently one or more of halogen, loweralkylthio, loweralkylsulfonyl, lower alkoxy, oxazol-2-yl, phenoxy; imidazol-1-yl; lower alkyl substituted imidazol-1-yl; or tert-butyl;

X^2 is a bond, -O-,



-S-,



or $-SO_2-$;

Q^2 is lower alkanediyl of 5, 6 or 7 carbon atoms optionally substituted by -OH; loweralkynediyl of 6-8 carbon atoms; or methylcyclohexylmethyl;

Y^2 is a bond, -S- or $-SO_2$; and

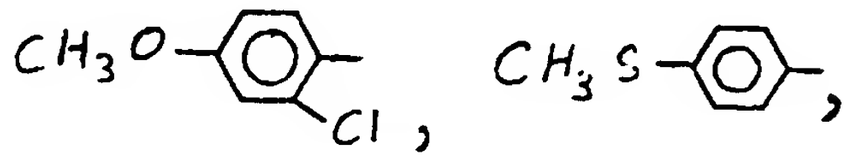
W^2 is imidazol-1-yl; substituted imidazol-1-yl wherein the substituents are independently one or more of loweralkyl, hydroxy loweralkyl, aminoloweralkyl and lower alkoxycarbonyl; imidazol-2-yl; imidazol-4-yl; imidazol-5-yl; substituted imidazol-2-yl, -4-yl or -5-yl, wherein the substituents are independently one or more of lower alkyl, and allyloxycarbonylmethyl; pyrrolidin-1-yl; benzimidazol-1-yl; 1,4 dihydro-4-oxo-7-methyl-1,8-3-carboxyl-naphthyridin-1-yl; purin-9-yl; pyridin-2-yl; pyrazol-1-yl; or benzimidazol-2-yl.

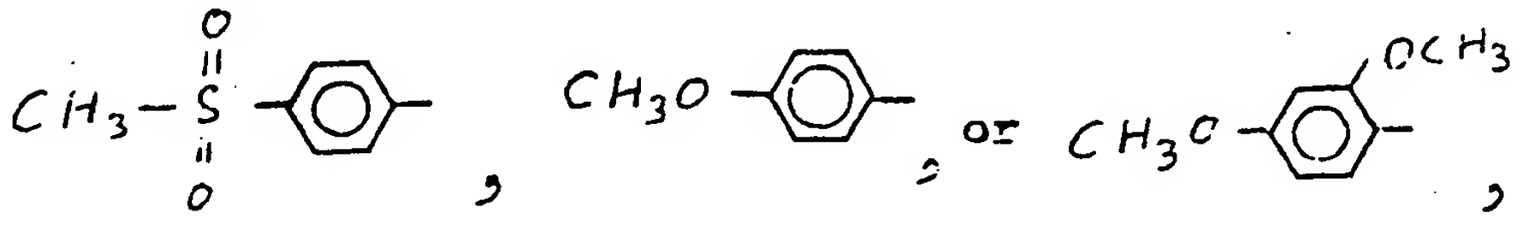
The most preferred compounds having PAF activity are represented by the following formula VI

Z^3-X^3-Q^3-W^3 III

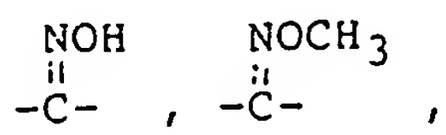
and pharmaceutically acceptable acid addition or quaternary salts thereof, wherein

Z^3 is

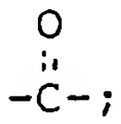




X^3 is

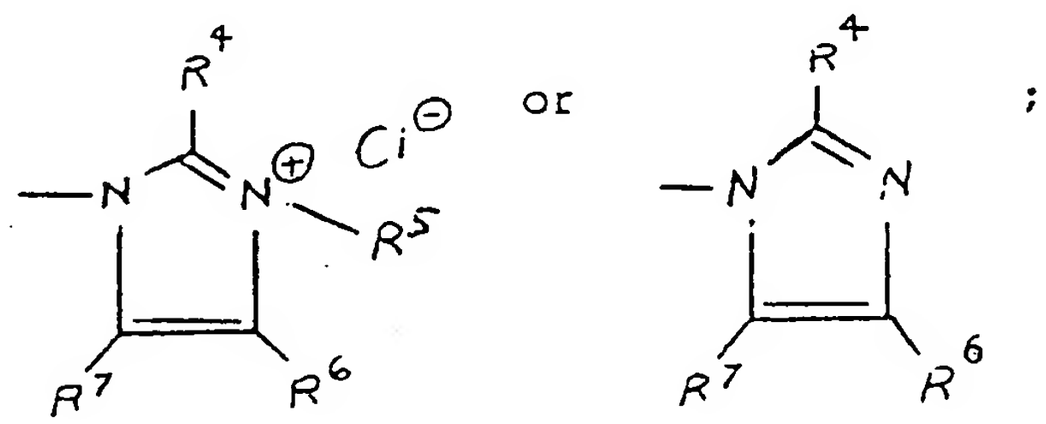


-S-, -O-, or



Q^3 is lower alkanediyl of 5, 6 or 7 carbon atoms optionally substituted by -OH;

W^3 is



and

R^4 is hydrogen, loweralkyl or hydroxy loweralkyl;

R^5 is lower alkyl;

R^6 and R^7 are independently one or more of hydrogen, loweralkyl, amino loweralkyl or nitro.

The compounds of this invention are conventionally formulated for oral, parenteral, topical and transdermal use, oral is preferred.

This invention includes within its scope pharmaceutical compositions comprising the compounds of this invention in admixture with a pharmaceutically acceptable carrier therefor. In addition, the present invention also includes the use of the compounds of formulas I and II for preparing pharmaceutical compositions useful for treating viral infections or inflammation, or for inhibiting platelet activating factor. In the foregoing compositions, the active compounds of this invention can be used alone as the sole active antiviral agent, sole active antiinflammatory agent or sole active PAF antagonist, or in combination with other therapeutic agents.

For the preferred oral administration, the compounds of this invention are typically formulated in the form of tablets, capsules, elixirs, solutions, suspensions and the like preferably solutions. For parenteral administration, they may be formulated into solutions or suspensions. Topical formulations such as lotions, creams, ointments, sprays and mechanical delivery devices, e.g. transdermal can also be made with the compounds of this invention.

Typical pharmaceutically acceptable carriers for use in the formulations described above are exemplified by: sugars such as lactose, starches such as corn starch, cellulose and derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and methyl cellulose; and other carriers well known in the art. The compositions may also contain preservatives, aerosol propellants and coloring, thickening, suspending, dispensing, emulsifying, wetting, stabilizing and buffering agents.

The dosage of the compounds of this invention which is administered is dependent, in the judgment of the attending clinician, upon a variety of factors, e.g. the age and weight of the individual being treated, the mode of administration, the potency of the administered compound, the indication for which the drug is administered and the severity of the ailment being treated.

Typically, the dosage administered per day for treating viral infections will be oral administration of from about 1 mg/kg to about 75 mg/kg daily in single or divided doses, with about 1-25 mg/kg preferred. The dosage for treating inflammation is about 25 mg to about 2 gm administered daily in divided doses, with the preferred range being about 25 to about 100 mg.

In order to achieve PAF antagonism, oral administration daily in single or divided doses of about 2.5 mg/kg to about 50 mg/kg can be used, preferably about 2.5 mg/kg to about 25 mg/kg. Intravenous administration can be about 0.5 mg/kg to about 10 mg/kg per day with 0.5 mg/kg to about 5 mg/kg preferred.

The compounds of this invention are prepared by the following methods:

(A) to produce a compound of formula I, a compound of the formula

$$Z\text{-}X\text{-}Q'\text{-}L^1$$

wherein Z and X are as defined previously,

Q' is the same as Q defined previously, or, provided Q in formula I is to contain at least one of the group

$$-\underset{\displaystyle R}{\overset{\displaystyle |}{CH}}-$$

wherein each R is independently hydrogen or lower alkyl, Q' may also be the same as Q defined above minus at least one of the groups

$$-\underset{\displaystyle R}{\overset{\displaystyle |}{CH}}-,$$

and

L^1 is a leaving group, with a compound having the formula

$$L^2\text{-}Y'\text{-}W''$$

where L^2 is a leaving group,

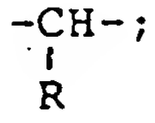
W'' is as defined for W in formula I, or a tautomer thereof, and

Y' is the same Y defined in formula I, or, provided Q in formula I is to contain at least one of the groups

$$-\underset{\displaystyle R}{\overset{\displaystyle |}{CH}}-$$

wherein each R is independently hydrogen or lower alkyl, Y' may also be the same as Y defined in

formula I plus at least one of the groups



or

(B) to produce a compound of formula II and possibly a compound of formula I, at least one compound of the formula

$Z\text{-}X\text{-}Q'\text{-}L^1$

wherein Z, X, Q' and L^1 are as defined previously is reacted with a compound of the formula

$L^3\text{-}Y'\text{-}W'''\text{-}Y'\text{-}L^4$

wherein L^3 and L^4 are leaving groups

each Y' is independently as defined above, and

W''' is divalent W' as defined above, or

(C) to produce a compound of formula I wherein Z and W are the same and X and Y are the same, reacting a compound of the formula

$L^2\text{-}Y'\text{-}W''$

wherein Y' and W'' are as defined previously and

L^2 is a leaving group, with a compound of the formula

$L^5\text{-}Q''\text{-}L^6$

wherein L^5 and L^6 are leaving groups and Q'' is divalent Q' as defined above,

wherein in the above processes, any reactive groups are protected if necessary or desired,

the above processes followed, if necessary or desired. by

(i) removal of any protecting groups,

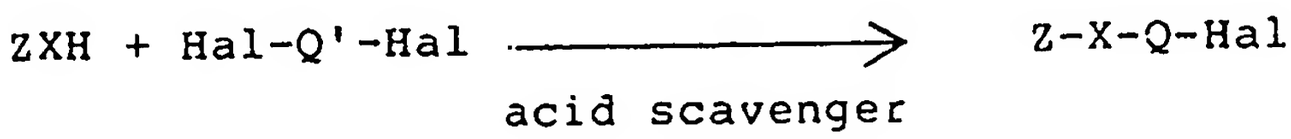
(ii) conversion of a compound so produced to another compound of formula I or formula II,

(iii) if more than one compound of formulas I or II is produced, separation of the compounds so produced, or

(iv) conversion of any of the compounds so produced to an acid addition, basic addition, or quaternary amine salt or pharmaceutically acceptable solvate thereof.

In process (A), L^1 is preferably bromine or most preferably iodine and L^2 is a preferably alkali metal such as sodium, potassium or cesium. The reaction takes place at temperatures of from about -20 °C to 60 °C in an inert organic solvent such as dimethylsulfoxide (DMSO), dimethylformamide (DMF) or tetrahydrofuran (THF). In most cases the final compounds can be converted to water-soluble acid addition or quaternary salts by conventional reactions, e.g., with hydrochloric acid or a quaternizing agent such as methyl sulfonic acid.

The starting compounds $Z\text{-}X\text{-}Q'\text{-}L^1$ wherein L^1 is halogen (Hal) are prepared by the following reaction:



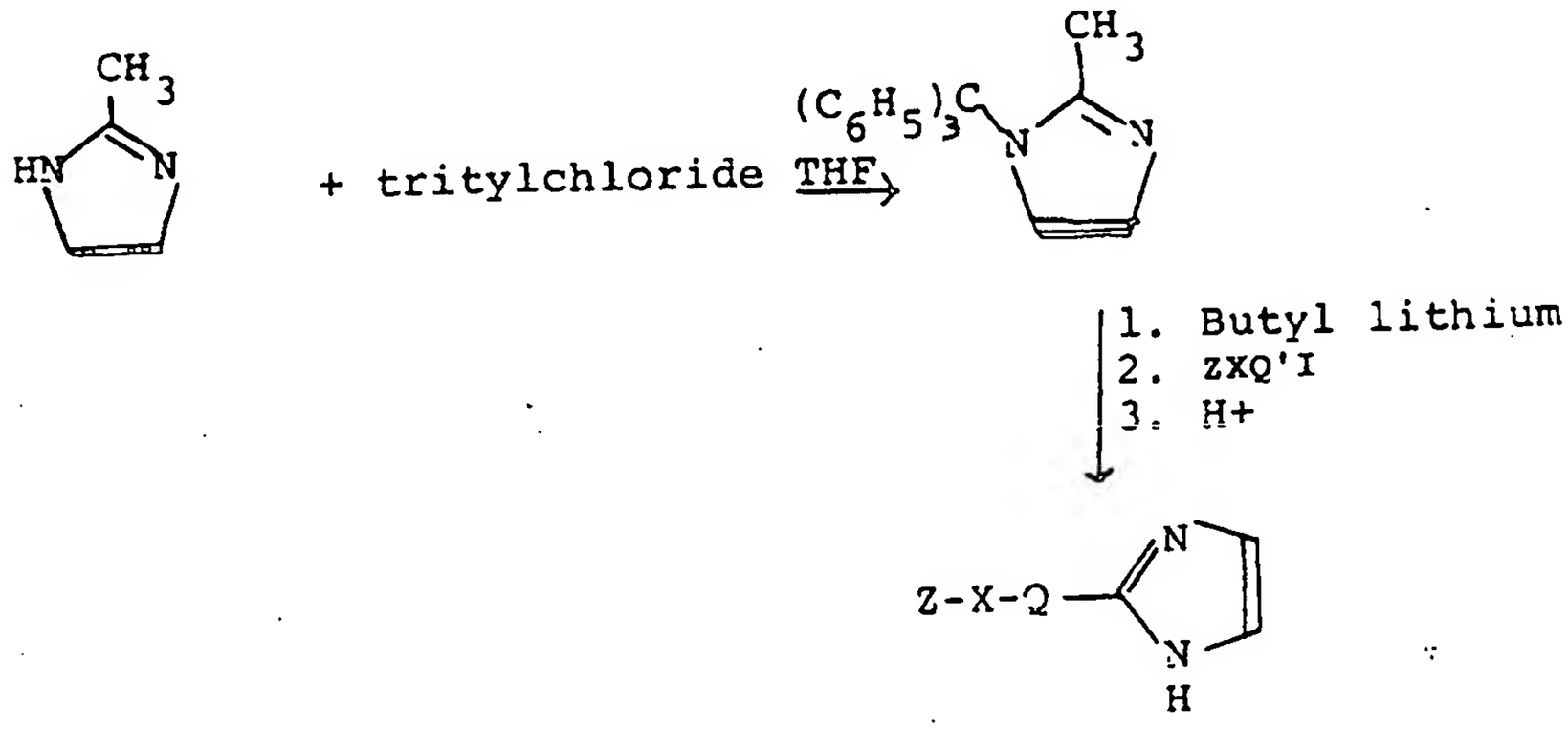
wherein Z, X and Q' are as defined above.

The reaction takes place in the presence of an acid scavenger such as K_2CO_3 or organic bases such as collidine and also Hunigs base. The preferred Hal group is iodine although bromine can also be used. The compound Hal-Q'-Hal wherein Hal is iodine can be prepared by reacting Br-Q'-Br with sodium iodide except when Q is $-CH_2-$ or $-CH_2-CH_2-$.

Alternatively ZXQ'-I can be prepared by reacting ZXH with Br-Q'-Br to obtain ZXQ'Br, then reacting ZXQ'Br with sodium iodide to obtain Z-X-Q'-I. Or for compounds when Q' is $-CH_2-$ or $-C_2H_4-$, Z-X-Q'-I can be prepared by reacting the corresponding mono or dihydric alcohol with HI.

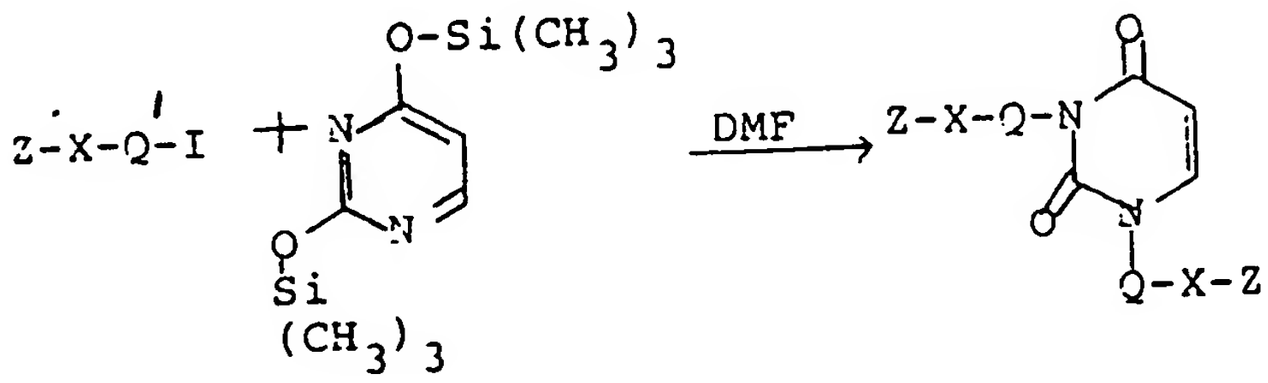
When W is a nitrogen containing heterocyclic moiety, the processes described above result in the W moiety being substituted at a nitrogen atom of the heterocyclic ring, unless the nitrogen atom is protected. In order to make a compound wherein the heterocyclic is substituted at a ring carbon, it is necessary to protect the nitrogen with a group which is easily removed after the C-substitution is carried out and is not removed during the C-substitution reaction, e.g., the trityl group.

Thus, for example, in the preparation of a 2-substituted imidazole, the following reaction scheme is followed:



wherein Q, Q', Z and X are as defined above. In this case the methyl group on the imidazo ring becomes part of Q in the compound produced.

In process (B) to make a compound of formula II, the W' moiety should have two ring carbons initially substituted with trimethylsilyloxy groups. When the reaction with Z-X-Q'-I is conducted, the resulting product is a disubstituted W' moiety as shown in the following reaction in which the trimethylsilyloxy substituted compound is illustrated as a pyrimidine.



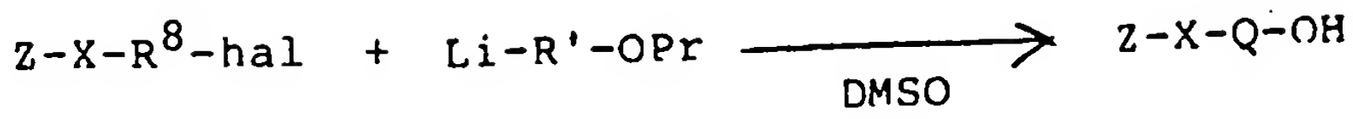
The reaction is carried out at room temperature.

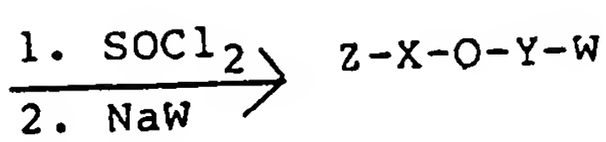
In process (B) if an excess of the compound Z-X-Q'-L^1 is used, the product will primarily be of formula II. However, if only small amounts of the compound Z-X-Q'-L^1 is used, products of formulas I and II will be produced. The reaction conditions are the same as in process (A).

To produce a compound of formula II wherein at least one of Z, X or Q is not identical with the other Z, X or Q two different compounds having the general formula Z-X-Q'-L^1 are used. The result is a mixture of compounds, which may be isolated by standard techniques.

Process C, which produces compounds of formula I wherein Z and W are the same and X and Y are the same, is carried out under the same reaction conditions as process (A).

The preparation of compounds wherein Q is an unsaturated chain, i.e. an alkynediyl or alkenediyl, is illustrated in the following reaction:



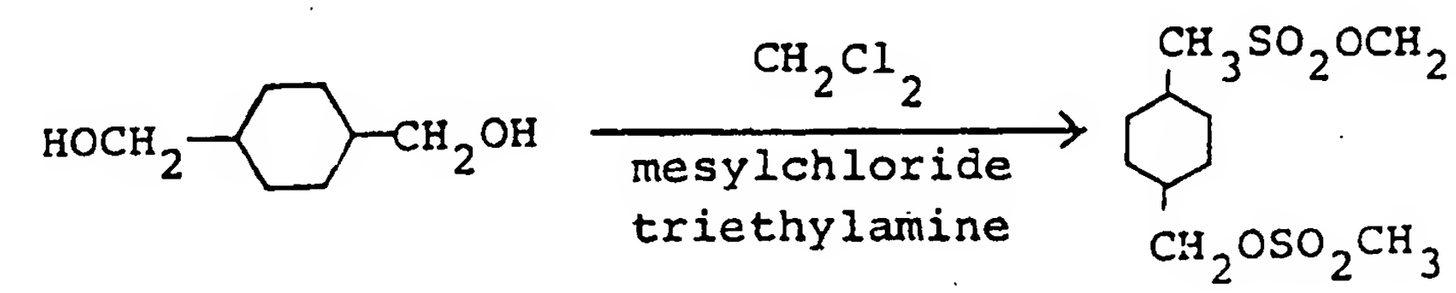


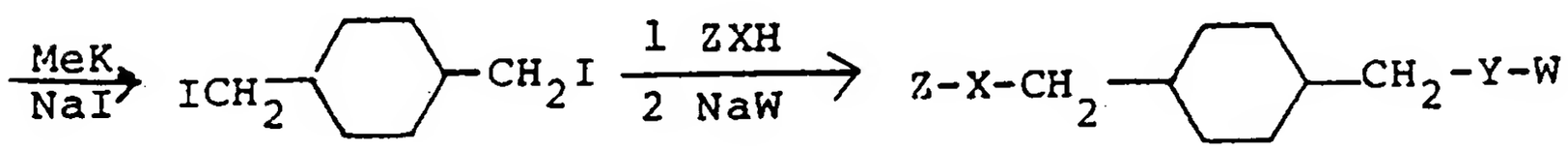
I

wherein R^8 is lower alkyl of 2 to 4 carbons and R' is lower alkynyl of 3 carbons, Y is a bond, Pr is a hydroxy protecting group and hal is bromine or iodine.

The alkenediyl is prepared by partially reducing the alkynediyl compound by catalytic hydrogenation.

The preparation of compounds in which Q is an alkyl having a cycloalkane in the chain is illustrated by the following reaction:





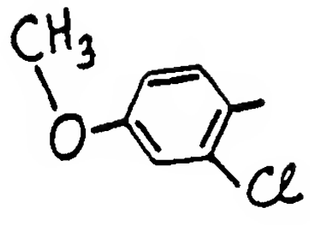
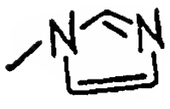
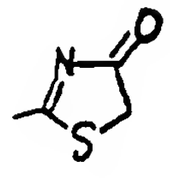
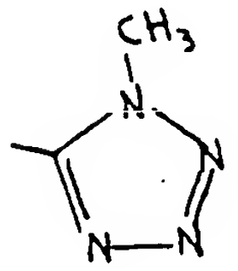
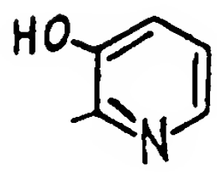
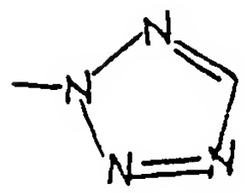
wherein hal is bromine or iodine and Z, X, Y and W are as defined above for formula I.

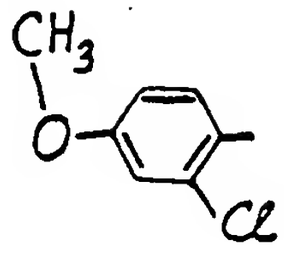
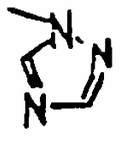
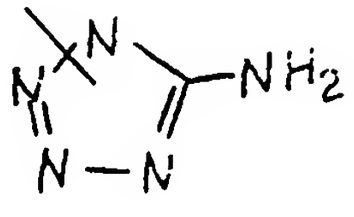
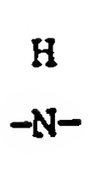
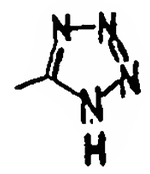
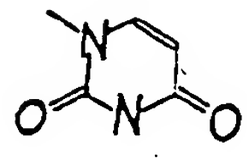
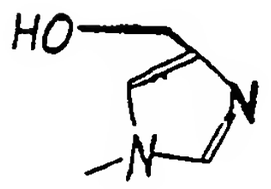
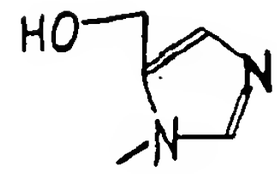
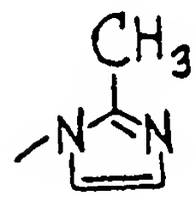
A compound of formula I or II can be converted to a different compound of formula I or II, respectively, by standard techniques well known in the art. Such conversion techniques are illustrated in the examples.

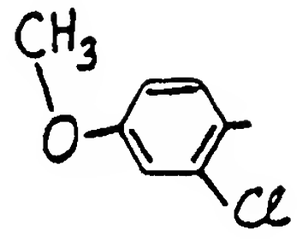
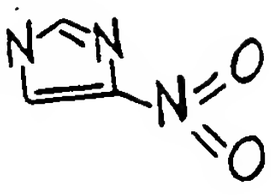
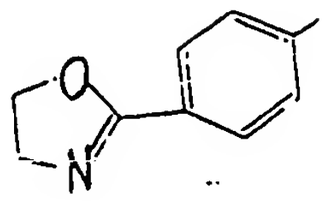
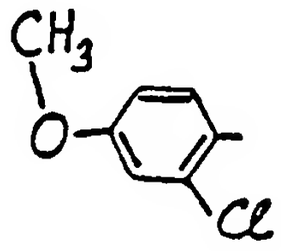
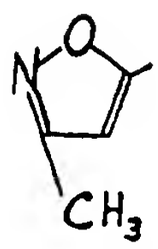
In general preparing the compounds of this invention involves relatively simple procedures as illustrated by the many examples which appear later in this text.

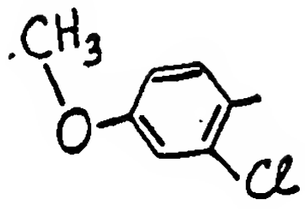
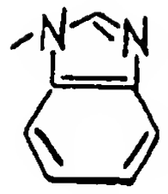
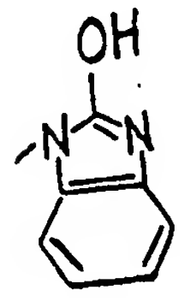
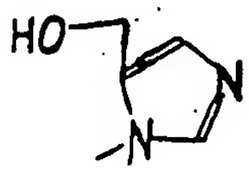
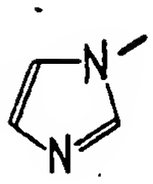
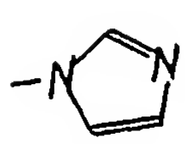
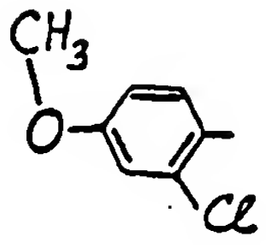
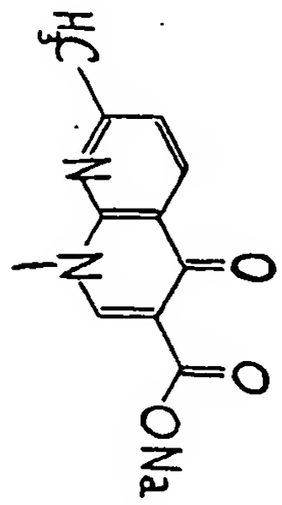
The following Table I shows the compounds of formula I prepared by the processes described above.

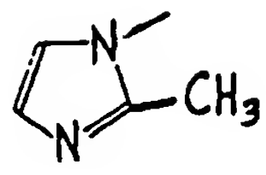
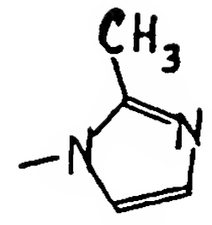
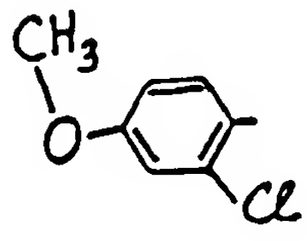
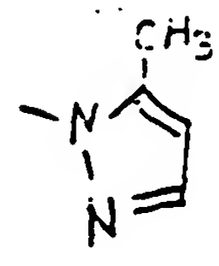
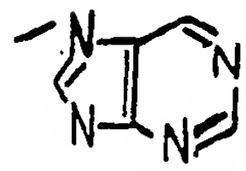
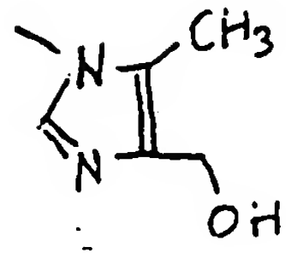
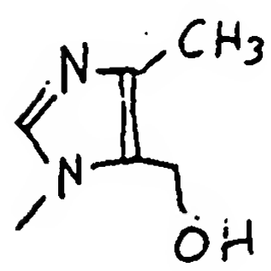
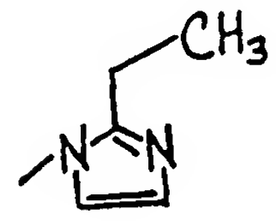
Table I

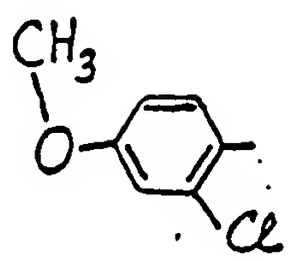
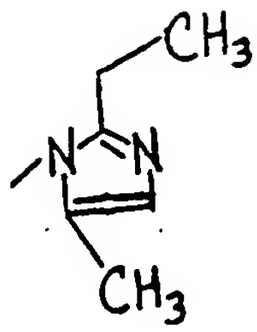
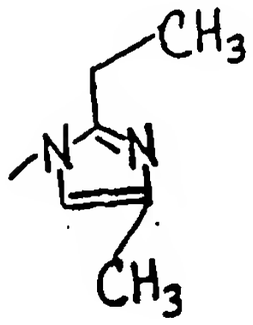
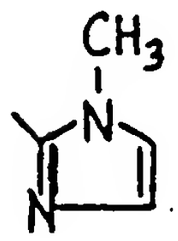
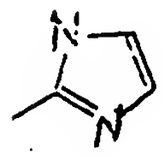
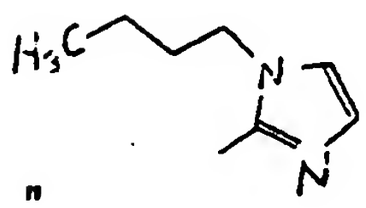
Example	Z	X	Q	Y	W	Salt
1.		-O-	$-(CH_2)_6-$	bond		HCl
2.	"	"	"	-S-		—
3.	"	"	"	"		—
4.	"	"	"	-S-		—
5.	"	"	"	bond		—
5A.	"	"	"	"		—

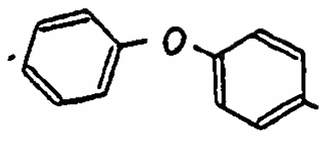
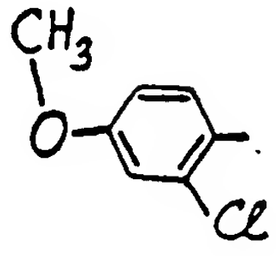
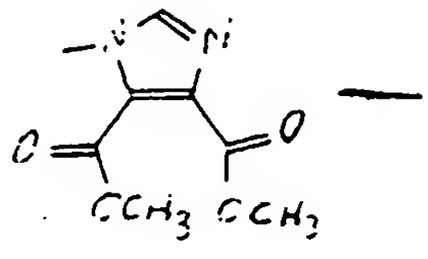
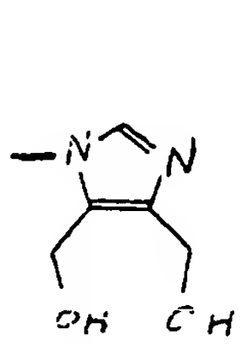
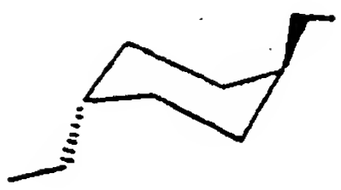
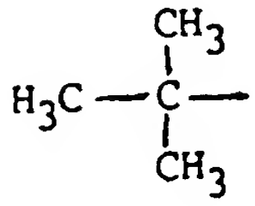
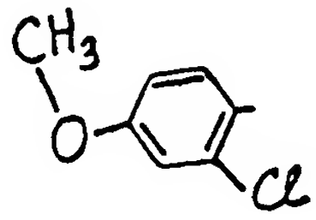
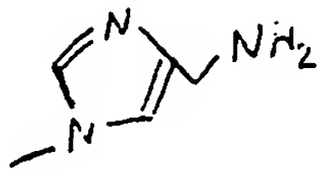
Example	Z	X	Q	Y	W	Salt
6.		-O-	$-(CH_2)_6-$	bond		—
7.	"	"	"	"		—
7A.	"	"	"			—
9.	"	"	"	bond		—
10.	"	"	"	"		HCl
10A.	"	"	"	"		"
11.	"	"	"	"		"

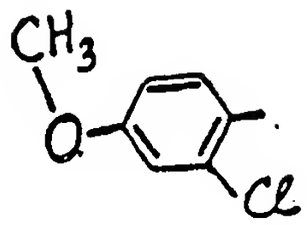
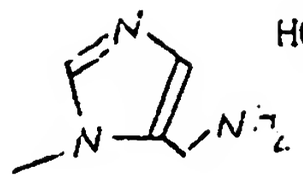
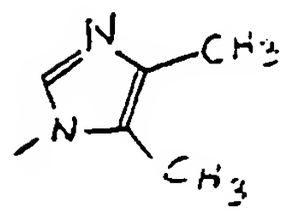
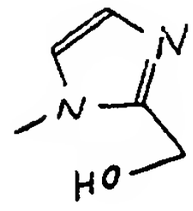
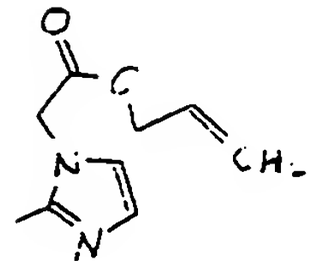
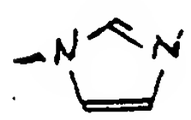
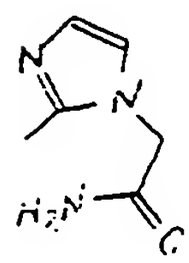
Example	Z	X	Q	Y	W	Salt
12.		-O-	$-(CH_2)_6-$	bond		—
13.	"	"	$-(CH_2)_7-$	"		HCl
14.		"	$-(CH_2)_6-$	"		"
15.		"	$-(CH_2)_7-$	"	"	"
16.	"	"	$-(CH_2)_5-$	"	"	"
17.	"	"	$-(CH_2)_{10}-$	"	"	"
18.		bond	$-(CH_2)_7-$	"	"	"

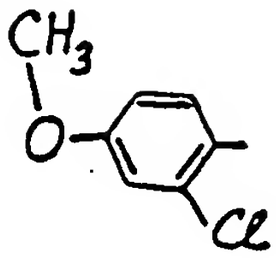
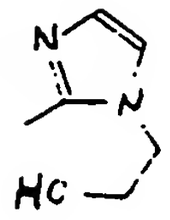
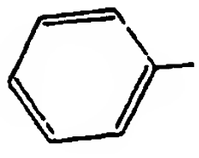
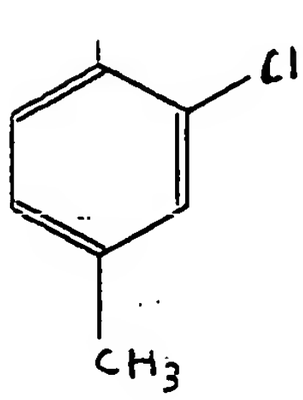
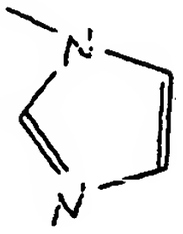
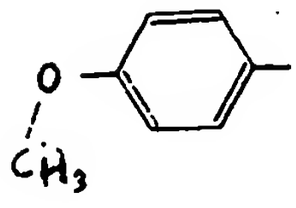
Example	Z	X	Q	Y	W	Salt
19.		-O-	$-(CH_2)_6-$	"		HCl
20.	"	"	"	"		—
21.	"	"	"	"		HCl
21A.	"	"	"	"		"
22.	"	"	"	"		"
23.		bond	"	"		"
24.		-O-	"	"		—

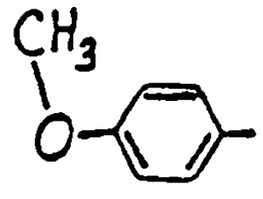
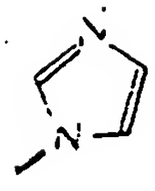
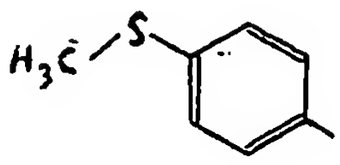
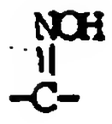
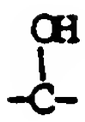
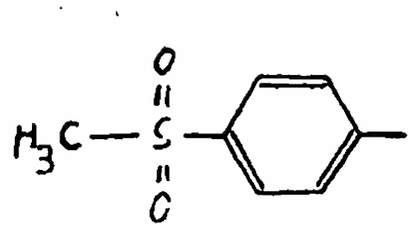
Example	Z	X	Q	Y	W	Salt
25.		bond	$-(CH_2)_6-$	bond		HCl
26.		-O-	"	"		—
27.	"	"	"	"		—
27A.	"	"	"	"		—
28A.	"	"	"	"		HCl
28.	"	"	"	"		"
29.	"	"	"	"		"

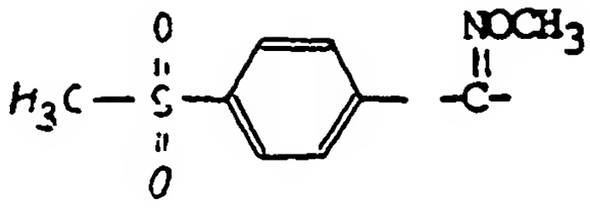
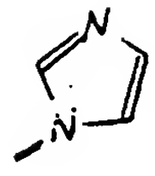
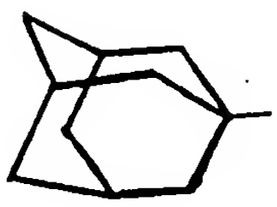
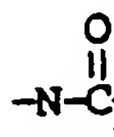
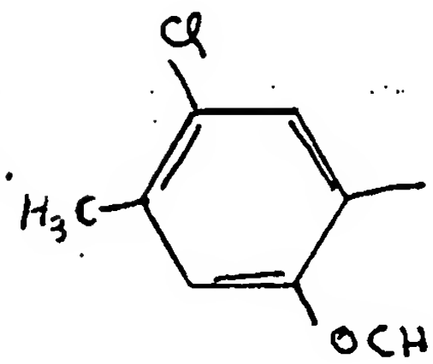
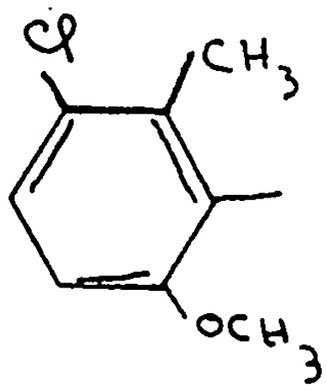
Example	Z	X	Q	Y	W	Salt
30.		-O-	$-(CH_2)_6-$	-S-		—
31.	"	"	"	bond		HCl
31A.	"	"	"	"		"
32.	"	"	$-(CH_2)_3-$	"		"
33.	"	"	$-(CH_2)_7-$	"		"
34.	"	"	"	"		"
35.	"	"	"	"		"

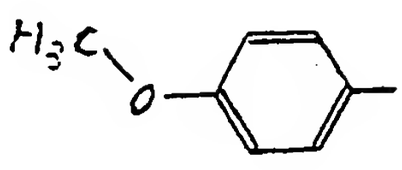
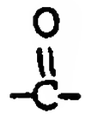
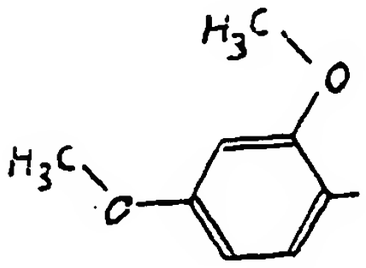
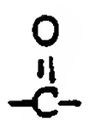
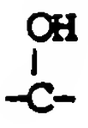
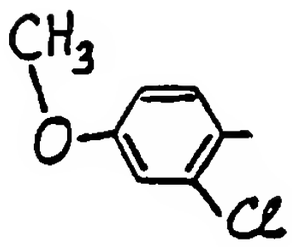
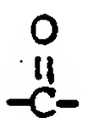
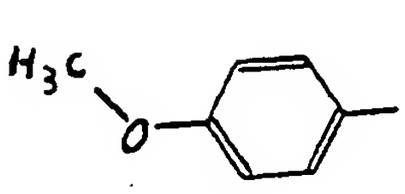
Example	Z	X	Q	Y	W	Salt
36.		-O-	$-(CH_2)_6-$	bond		HCl
37.		"	"	"		—
38.	"	"	"	"		HCl
39.	"	"		"		"
40.		bond	$-C\equiv C-(CH_2)_6-$	"	"	"
41.		-O-	$-(CH_2)_6-$	"		I^-
42.	"	"	"	"		HCl

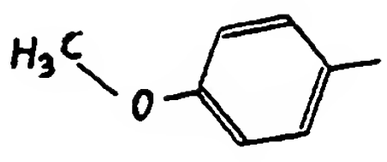
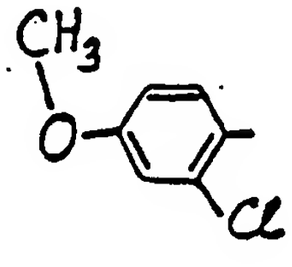
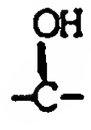
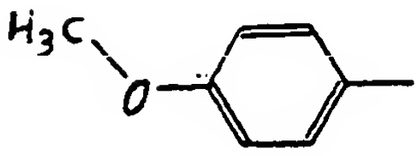
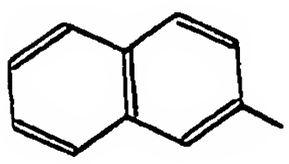
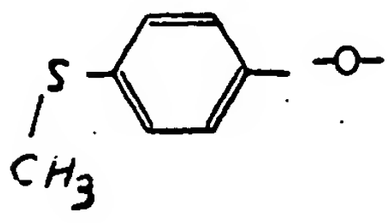
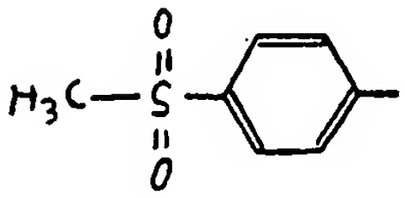
Example	Z	X	Q	Y	W	Salt
42. A		-O-	$-(CH_2)_6-$	bond		HCl
43.	"	"	"	"		"
44.	"	"	"	"		"
45	"	"	$-(CH_2)_7-$	"		"
46.	"	"	"	"		—
47.	"	"	$-(CH_2)_3-C\equiv C-CH_2-$			HCl
48.	"	"	$-(CH_2)_7-$			"

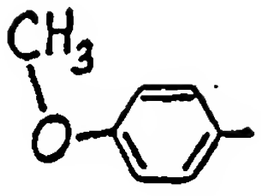
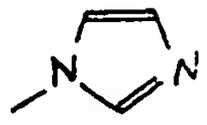
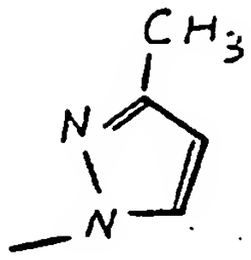
Example	Z	X	Q	Y	W	Salt
49.		-O-	$-(CH_2)_7-$	bond		HCl
50.		bond	$-C\equiv C(CH_2)_6-$	bond		"
51.			$-(CH_2)_5-$	bond		"
52.			$-(CH_2)_6-$	bond	"	"
53.	"		"	"	"	"
54.	"	bond	$-CH=CH(CH_2)_5-$	"	"	"

Example	Z	X	Q	Y	W	Salt
55.			$-(CH_2)_6-$	"		HCl
56.	"	bond	$-(CH_2)_7-$	"	"	"
57.			$-(CH_2)_6-$	"	"	"
58.	"			"	"	"
59.	"			"	"	—
60.				"	"	HCl

Example	Z	X	Q	Y	W	Salt
61.			$-(CH_2)_7$	bond		HCl
62.	"		"	"	"	"
63.	"		"	"	"	"
64.			$-(CH_2)_5-$	"	"	"
65.		bond	$-(CH_2)_6-$	"	"	"
65A.		"	"	"	"	"

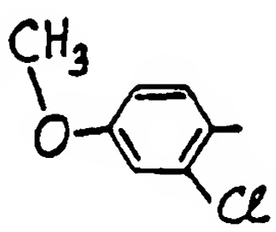
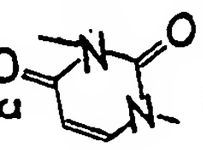
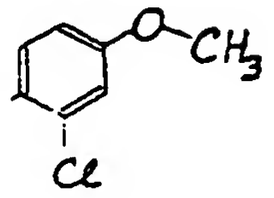
Example	Z	X	Q	Y	W	Salt
66.			$-(CH_2)_5-$	bond		HCl
67.			"	bond	"	"
68.	"		"	"	"	——
69.	"	bond	$-CH=CH(CH_2)_4-$	"	"	HCl
70.			$-(CH_2)_5-$	"	"	"
71.			"	"	"	——

Example	Z	X	Q	Y	W	Salt
72.		bond	$-CH=CH(CH_2)_4$	bond		HCl
73.			$-(CH_2)_5-$	"	"	---
74.		bond	$-(CH_2)_6-$	"	"	HCl
75.		-O-	$-(CH_2)_6-$	"	"	"
76.		-O-	$-(CH_2)_6-$	"	"	"
77.		"	"	"	"	"

Example	Z	X	Q	Y	W	Salt
78.		-S-	$-(CH_2)_6-$	bond		HCl
79.	"	$-SO_2-$	"	"	"	"
26A.	"	-O-	"	"		"

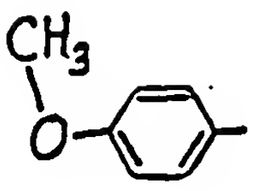
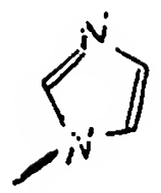
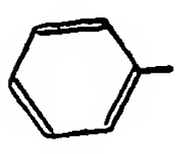
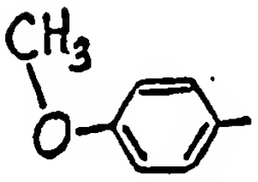
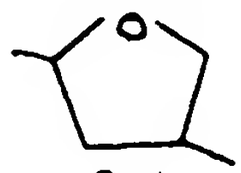
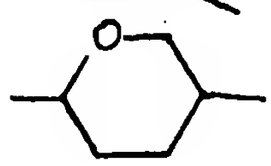
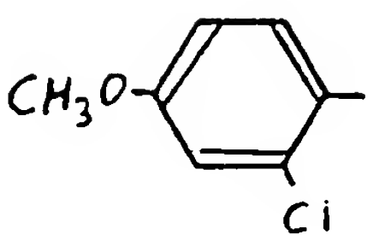
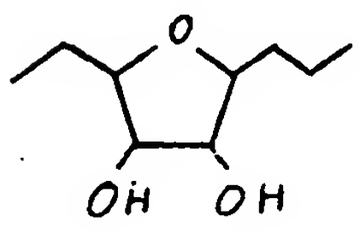
The following Table II shows the components of the compounds of Formula II.

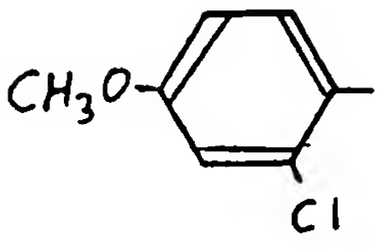
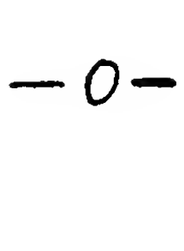
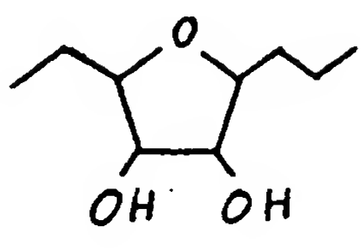
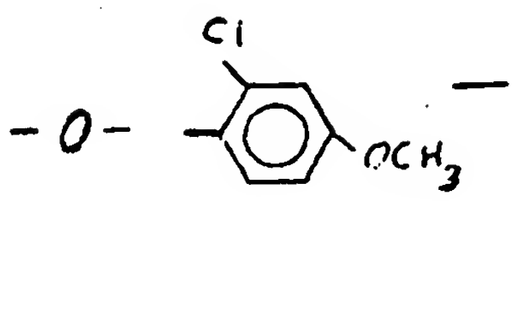
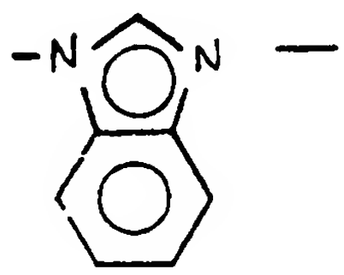
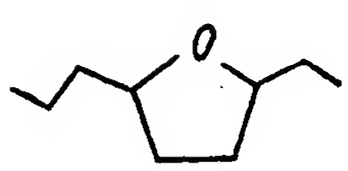
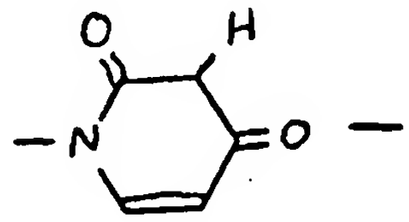
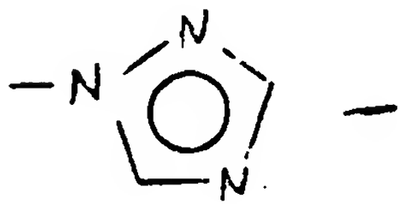
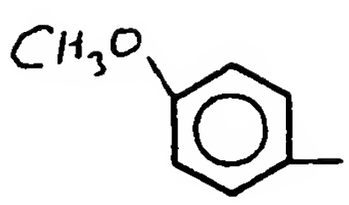
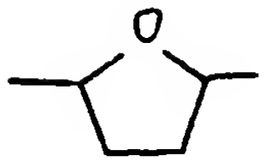
Table II

Example	Z	X	Q	Y	W'	Y	Q	X	Z
8.		-O-	$-(CH_2)_6-$	bond		bond	$-(CH_2)_6-$	-O-	
20.	"	"	"	"		"	"	"	"

The following Table III shows additional compounds which can be prepared by following the procedures of the examples which follow by substituting the appropriate starting materials for those in the examples.

Table III

Z	X	Q	Y	W	Salt
		$-(CH_2)_6-$	bond		HCl
	bond	$-(CH_2)_6-C\equiv C-$	"	"	"
	"	$-(CH_2)_6-C\equiv C-$	"	"	"
"	"		"	"	"
"	"		"	"	"
"	"		"	"	"
	— O —		"		—
"	"	"	"		—
"	"	"	"		—

Z	X	Q	Y	W	Salt
					
〃	〃	〃	〃	bond 	
〃	〃		〃		
〃	〃	〃	〃		
〃	〃	〃	〃		
	bond		〃	〃	HCl

The starting materials for use in the preparation of the compounds of this invention are either commercially available or are prepared by conventional means known in the art.

The following examples illustrate the invention. Fast atom bombardment (FAB) mass spectra (MS) were run on a Finnigan MAT 312 double focussing mass spectrometer, operating at an accelerating voltage of 3 kV. The MS samples were ionized by bombardment with xenon atoms produced by a saddle field ion source from Ion Tech operating with a tube current of 2 mA at an energy of 6 KeV. The proton nuclear magnetic resonance (H^1-NMR) spectra were recorded at 200 MHz on a Varian XL-200 spectronometer; all chemical shift values δ are reported in ppm downfield from tetramethylsilane.

EXAMPLE 1

1-[6-(2-chloro-4-methoxyphenoxy)hexyl]imidazole

Add 200 mg. 6-(2-chloro-4-methoxyphenoxy)hexyl-1-bromide in 1.5 ml of dimethyl formamide (DMF) to 180 mg sodium imidazole in a reaction vial at room temperature, stir 2 hours then add 20 mg sodium iodide, stir overnight. Add methylene chloride, wash with water then brine, elute on a coarse silica column with methylene chloride then a mixture of 50% ethylacetate and methylene chloride (v/v) to isolate the title compound.

EXAMPLE 2

2-([6-(2-chloro-4-methoxyphenoxy)hexyl]thio) -4,5-dihydrothiazol-4-one

(a) Reflux about 500 mg sodium iodide in 10 ml of acetone with 350 mg. 6-(2-chloro-4-methoxyphenoxy)-hexyl-1-bromide for 5 to 10 minutes, remove the acetone by bubbling nitrogen through the reaction mixture, add methylene chloride, wash with water, then brine and dry over sodium sulfate to obtain 6-(2-chloro-4-methoxyphenoxy)hexyl-1-iodide.

(b) Add 3 grams of 6-(2-chloro-4-methoxyphenoxy)hexyl-1-iodide in 10 ml acetonitrile to 1.2 g rhodanine and 20 g cesium carbonate. Stir overnight, then remove the acetonitrile, add methylene chloride and wash with water then brine and dry over sodium sulfate. Elute on a coarse silica column with methylene chloride followed by 5% ethylacetate/methylene chloride and finally 10% ethylacetate/methylene chloride to yield the title compound isolation.

EXAMPLE 3

5-{[6-(2-chloro-4-methoxyphenoxy) hexyl]thio}-1-methyltetrazole

Reflux 350 mg. 6-(2-chloro-4-methoxyphenoxy) hexyl-1-bromide with 10 ml of acetone and about 500 mg. sodium iodide for five to ten minutes, remove the acetone by bubbling nitrogen through the reaction mixture, add methylene chloride, wash with water, then brine and dry over sodium sulfate to obtain 6-(2-chloro-4-methoxyphenoxy)hexyl-1-iodide. Add 133 mg of 5-mercapto-1-methyltetrazole, 268 mg. cesium carbonate and 3 ml acetonitrile to the iodide product, stir overnight, add methylene chloride and wash with water, sodium carbonate, water, then brine and dry over sodium sulfate. Remove the solvent and recover the title compound as crystals.

EXAMPLE 4

2-{[6-(2-chloro-4-methoxyphenoxy) hexyl]-thio}-3-pyridinol

Stir 300 mg. of the iodide prepared in Examples 2 or 3, 3 ml. acetonitrile 112 mg. 2-mercapto-3-pyridinol and 201 mg. cesium carbonate in a reaction flask overnight at room temperature. Remove the acetonitrile and add methylene chloride. Wash with sodium carbonate solution, water, then brine and dry over sodium sulfate. Remove the solvent then add methylene chloride, heat to dissolve the mixture, add hexane and cool to precipitate the title compound as white crystals.

EXAMPLE 5

1 and 2-[6-(2-chloro-4-methoxyphenoxy)hexyl]tetrazole

Stir overnight at room temperature 300 mg. of the iodide prepared in Examples 2 and 3, 3 ml. acetonitrile, 63 mg. 1-H-tetrazole and 274 mg. cesium carbonate in a reaction flask. Add an additional. 189 mg. 1-H-tetrazole and 100 mg. cesium carbonate, let stir one week at room temperature. Work up the reaction mixture in methylene chloride with a water wash. Elute on a coarse silica column with methylen chloride then ethyl acetate/methylene chloride. Isolate two fractions of the title compound, the less polar fraction and the more polar fraction. One of the fractions is the 1-substituted tetrazole and the other fraction is the 2-substituted tetrazole.

EXAMPLE 6

1-[6-(2-chloro-4-methoxyphenoxy) hexyl]-1,2,4-triazole

Stir overnight at room temperature, 300 mg. of the iodide prepared in Examples 2 or 3, 3 ml. acetonitrile, 225 mg. 1,2,4-triazole and 274 mg. cesium carbonate in a reaction flask. Work up the reaction mixture in methylene chloride with a water wash and elute on a silica column with methylene chloride and ethylacetate to recover the title compound.

EXAMPLE 7

1 or 2-[6-(2-chloro-4-methoxyphenoxy) hexyl]-5-amino-tetrazole and 5-{[6-(2-chloro-4-methoxyphenoxy)-hexyl]-amino}-tetrazole

Stir overnight at room temperature, 300 mg. of the iodide prepared in Examples 2 or 3, 2 ml. dimethyl formamide DMF, 421 mg. 5-amino tetrazole and 274 mg. cesium carbonate. Test the product on thin layer chromatography (TLC) with 50% ethyl acetate/hexanes. The test indicates that two separate compounds resulted, one more polar than the other. Separate the less polar title compound and the more polar title compound on a coarse silica column by eluting with methylene chloride followed by 5% ethyl acetate/methylene chloride, then 10% ethyl acetate/methylene chloride. The more polar compound is highly crystalline. The less polar of the compounds is the 1 or 2 substituted tetrazole, and the more polar is the exocyclic nitrogen substituted tetrazole title compound.

EXAMPLE 8

1,3-di-[6-(2-chloro-4-methoxyphenoxy)hexyl] -1,2,3,4-tetrahydropyrimidine-2,4-dione

Stir overnight at room temperature, 300 mg. of the iodide prepared in Examples 2 or 3, 1.83 gm. 2,4 ditrimethylsilyloxypyrimidine, anhydrous DMF and 1.24 gm. cesium fluoride in a reaction flask. Work up with a water wash in methylene chloride, elute on a coarse silica gel column with methylene chloride followed by 10% ethyl acetate/methylene chloride then 20% ethyl acetate/methylene chloride to isolate the title compound.

EXAMPLE 9

1-[6-(2-chloro-4-methoxyphenoxy)hexyl] -1,2,3,4-tetrahydropyrimidine-2,4-dione

Stir overnight at room temperature, 300 mg. of the iodide made in Examples 2 or 3, 1 ml. acetonitrile, 274 mg. cesium carbonate, 270 mg. of 2N-benzoyl uracil, 1 ml. of DMF (to enhance solubility) and 100 mg. additional of cesium carbonate in a reaction flask. Work up in methylene chloride with water and add methanolic potassium carbonate then again stir overnight at room temperature. Work up in methylene chloride with a water wash. Elute on a coarse silica column with methylene chloride and sequently 10%, 20%, 30% and 40% ethyl acetate/methylene chloride to obtain the title compound as an oil which crystallizes upon standing.

EXAMPLE 10

1-[6-(2-chloro-4-methoxyphenoxy)hexyl]-4-and 5-hydroxymethylimidazole

Add 200 mg. of the iodide made in Examples 2 or 3 to 20 ml. DMF, then add 500 mg. NaOH and finally 200 mg. 4-hydroxymethyl imidazole to a reaction flask, stir at room temperature for about 24 hours.

Add methylene chloride and wash with water, then brine and dry over sodium sulfate. Elute on a coarse silica column with methylene chloride, then 5% methanol/methylene chloride, then 10% methanol/methylene chloride and isolate a mixture of the title compounds. The isomers are separated on TLC with thylacetate, and finally on a coarse silica column with 50% ethylacetate/THF to yield the title compounds as the less polar isomer in fractions 5-8 and the more polar isomer in fractions 11-18. Prepare the hydrochloride salts by reaction with 0.1N HCl.

EXAMPLE 11

1-[6-(2-chloro-4-methoxyphenoxy)hexyl]-2-methylimidazole

Stir about 5 hours at room temperature, 200 mg. of the iodide made in Examples 2 or 3, 134 mg. 2-methylimidazole, 3 ml. DMF and 69 mg. sodium hydroxide in a reaction flask. Work up in methylene chloride with a water wash, then brine, then dry over sodium sulfate to recover the title compound as an oil which crystallizes on standing. Prepare the hydrochloride salt by reaction with 0.1N HCl.

EXAMPLE 12

1-[6-(2-chloro-4-methoxyphenoxy) hexyl]-4-nitroimidazole

Stir overnight at room temperature, 200 mg. of the iodide made in Examples 2 or 3, 3 ml. DMF, 184 mg. 4-nitroimidazole and 69 mg. sodium hydroxide in a reaction flask. Work up with methylene chloride and a water wash. Elute on a coarse silica column with methylene chloride then ethylacetate to obtain the title compound.

EXAMPLE 13

2-[7-(2-chloro-4-methoxyphenoxy)heptyl] pyridine

Under a nitrogen atmosphere, add 152 mg. 2-picoline and 1.5 ml. tetrahydrofuran (THF) and cool to -28 • C. Add 104 mg. n-butyl lithium and stir about 30 minutes at -78 • C. Add 20 mg. of the iodide prepared in Examples 2 and 3 in 1 ml. THF. Stir 1 hour at -78 • C, let warm to room temperature and stir about 15 hours. Work up with water and methylene chloride then wash with water and brine then dry over sodium sulfate. Elute on a coarse silica column with methylene chloride then 50% ethylacetate/methylene chloride to obtain the title compound. Prepare the hydrochloride salt by reaction of the title compound with 0.1N HCl.

EXAMPLE 14

1-{6-[4-(4,5-dihydro-2-oxazolyl) phenoxy]hexyl}imidazole

(a) Prepare 6-[4-(4,5-dihydro-2-oxazolyl)-phenoxy]-hexyl-1-iodide by adding 10 gm. of 4-(4,5-dihydro-2-oxazolyl)phenol, 24.4 gms.. 1,6-dibromohexane, 10 gm. sodium iodide, 35 gm potassium carbonate and 250 ml. acetonitrile in a reaction flask. Purge with nitrogen, reflux for 24 hours, cool and filter off resulting solid. Remove acetonitrile and extract with ethylacetate. Remove the ethylacetate to yield an oil/solid. Purify on silica with methylene chloride to recover the product.

(b) Add 200 mg. of the product from part (a), 300 mg. of sodium imidazole and 10 ml. of dimethylformamide (DMF) to a flask and stir for 48 hours. Partition the reaction mixture water/methylene chloride. Elute on a silica column with 100% ethylacetate followed by 10% methanol/methylene chloride to yield the title compound.

Prepare the hydrochloride salt by adding 6 ml. of 0.1N HCl.

MS: m/z 314 (M^+)

EXAMPLE 15

1-[7-(2-chloro-4-methoxyphenoxy) heptyl]imidazole

(a) Prepare 7-(2-chloro-4-methoxyphenoxy) heptyl-1-iodide by adding 3 gms. of 2-chloro-4-methoxyphenol, 9.8 gms. 1,7-dibromo heptane, and 5.2 gms. potassium carbonate to 75 ml. acetone in a reaction flask. Purge with nitrogen, reflux for 48 hours, cool. Add CH_2Cl_2 and wash with water, then brine and dry over sodium sulfate. Elute on a coarse silica column with hexane, 10, 15 and 20% CH_2Cl_2/hexane. Isolate product, add 50 ml. acetone, 8.5 g sodium iodide and heat to reflux 10-15 min. Remove acetone, add CH_2Cl_2 and wash with water, then brine and dry over sodium sulfate. Remove solvent and recover the product.

(b) Add 2 gms. of the product of step (a), 1.4 gms. sodium imidazole and DMF in a reaction flask, stir for about 24 hours. Work up with methylene chloride and a water wash, remove the solvent under a high vacuum and recover the title compound. Convert the title compound to the hydrochloride salt by reaction with 0.1N hydrochloric acid.

EXAMPLE 16

1-[5-(2-chloro-4-methoxyphenoxy)pentyl]imidazole

(a) Prepare 5-[2-chloro-4-methoxyphenoxy)pentyl-1-iodide by mixing 3 gms. 2-chloro-4-methoxyphenol, 8.7 gms. 1,5-dibromo pentane, and 5.2 gms. potassium carbonate to 75 ml. acetone in a reaction flask. Purge with nitrogen, reflux for 48 hours. Add CH_2Cl_2 and wash with water, then brine and dry over sodium sulfate. Elute on a coarse silica column with hexane, 10, 15 and 20% CH_2Cl_2/hexane. Isolate product, add 50 ml. acetone, 8.5 g sodium iodide and heat to reflux 10-15 min. Remove acetone, add CH_2Cl_2 and wash with water, then brine and dry over sodium sulfate. Remove solvent and recover the product.

(b) Add 350 mg. of the product of step (a) to 2 ml. DMF (dimethylformamide) and 300 mg. sodium imidazole in a reaction flask. Stir for about 24 hours. Recover the title compound by treating with methylene chloride, a water wash and brine. Dry over sodium sulfate and remove the solvent to obtain a crystalline compound.

Prepare the hydrochloride salt by reacting 275 mg. of the title compound with 10.2 ml. of 0.1N HCl.

EXAMPLE 17

1-[10-(2-chloro-4-methoxyphenoxy) decyl]imidazole

(a) Prepare 10-(2-chloro-4-methoxyphenoxy)decyl-1-iodide by adding 3 g of 2-chloro-4-methoxyphenol, 11.3 g of 1,10-dibromodecane, 75 ml acetone and 5.2 g potassium carbonate in a reaction flask. Reflux for 48 hours, cool and remove acetone. Add CH_2Cl_2, wash with water then brine and dry over sodium sulfate. Elute on a coarse silica column with hexane then 15 and 20% CH_2Cl/hexane to obtain the product. Take 3.6 g of 10-(2-chloro-4-methoxyphenoxy)decyl-1-bromide, 50 ml acetone and 7.1 g NaI and heat to reflux for 20 mins. Remove acetone, add methylene chloride and wash with water, then brine and dry over sodium sulfate. Remove methylene chloride and recover 10-(2-chloro-4-methoxyphenoxy)-decyl-1-iodide.

(b) Stir 0.5 gm. of the compound prepared in step (a), 10 ml. DMF and 160 mg. sodium imidazole in a reaction flask for about 24 hours at room temperature. Recover the resulting title compound by treating with methylene chloride, washing with water, then brine, drying over sodium sulfate and removing the solvent. The recovered title compound is crystalline.

Prepare the hydrochloride salt of the title compound by reacting 340 mg. with 33 mg. 0.1N HCl.

EXAMPLE 18

5-[7-(1-imidazolyl)-heptyl] -3-methylisoxazole

(a) Prepare 7-(3-methylisoxazole-5-yl)heptyl-1-bromide by adding 20 ml. of 3,5-dimethylisoxazole to 200 ml. THF (tetrahydrofuran) under nitrogen and cool to about -78 °C. Slowly add (over 10 minutes) 80 ml. of N-butyl lithium, 2.5M/hexane and stir for 30 minutes. Add the resulting solution to a solution of 244 gm. 1,6-dibromohexane in 100 ml. THF at -78 °C. Purge with nitrogen, stir in a dry ice/acetone bath and then allow to warm to room temperature over a period of about 3 hours. Recover the product from the solvent and unreacted starting materials by distillation under reduced pressure (1/2 mm Hg) b.p. 134-136 °C.

(b) Stir 260 mg. of the compound made in step (a) with 450 mg. sodium imidazole in 2 gms. DMF for one week at room temperature. Partition with water/methylene chloride, elute on a silica column with 100% methylene chloride followed by 100% ethylacetate to yield the title compound. Prepare the hydrochloride salt of the title compound by reaction with 0.1N HCl.

FAB-MS: m/z 248 (M^+) - base, HCl salt, H^1-NMR-200 mHz; $^\delta$H ($CDCl_3$) 1.37 (6H,s), 1.55-1.80 (2H,m), 1.80-2.00 (2H,m) 2.25 (3H,s), 2.70 (2H,t,J 8Hz), 4.35 (2H,t,J 8Hz), 5.85 (1H,s), 7.18 (1H,s), 7.40 (1H,s), 9.65 (1H,s).

EXAMPLE 19

1-[6-(2-chloro-4-methoxyphenoxy) hexyl]benzimidazole

Stir overnight at room temperature, 300 mg. of the iodide made in Examples 2 or 3, 3 ml. DMF, 145 mg. benzimidazole and 49 mg. sodium hydroxide. Treat with methylene chloride, wash with water, then brine and recover the title compound by removing the solvent.

The hydrochloride salt is made by reacting the title compound with about 1.1 eq. 0.1N HCl.

EXAMPLE 20

1-[6-(2-chloro-4-methoxyphenoxy)hexyl]-2-hydroxybenzimidazole and N,N'-bis-[6-(2-chloro -4-methoxyphenoxy)hexyl]-2-benzimidazolone

Stir overnight at room temperature, 1 gm. 2 hydroxybenzimidazole, 2 gms. of the iodide prepared in Examples 2 or 3, 0.35 gm sodium hydroxide and 10 ml DMF in a reaction flask. Partition with water/methylene chloride. Elute on a silica column with 100% methylene chloride, then 50/50 methylene chloride/ethylacetate. Two major fractions are obtained, NMR shows the top spot fraction to be N,N'-bis'-[6-(2-chloro-4-methoxyphenoxy)hexyl]-2-benzimidazolone, FAB-MS: m/z 615 (M^+) free base, H^1-NMR-200 mHz; δH ($CDCl_3$), 1.35-1.65 (8H,m), 1.70-1.90 (8H,m), 3.75 (6H,s), 3.80-4.05 (8H,m), 6.7-7.2 (10H,m), and the bottom spot fraction to be 1-[6-(2-chloro-4-methoxyphenoxy)hexyl]-2-hydroxybenzimidazole. FAB-MS: m/z 375 (M^+); Free Base, H^1-NMR-200 mHz; δH ($CDCl_3$), 1.4-1.70 (4H,m), 1.7-1.9 (4H,m), 3.75 (3H,s), 3.85-4.05 (4H,m), 6.7-7.2 (7H,m).

EXAMPLE 21

1-[6-(2-chloro-4-methoxyphenoxy) hexyl]-4-and-5-hydroxymethylimidazole

Stir overnight at room temperature, 3 gm. of the iodide prepared in Examples 2 or 3, 15 ml. DMF, 1.01 gm. sodium hydroxide and 1.64 gm. 4-hydroxymethyl imidazole HCl. Add methylene chloride and wash several times with water. Elute on a coarse silica column with methylene chloride, then 2% methanol/methylene chloride and finally 5% methanol/methylene chloride and obtain a mixture of the title compounds.

Prepare the hydrochloride salt by reacting the title compounds with about 1.1 eq. of 0.1N hydrochloric acid.

EXAMPLE 22

1-[6-(2-chloro-4-methoxyphenoxy)hexyl]pyrrolidine

Stir overnight at room temperature 500 mg. of the iodide prepared in Example 2 or 3, 5 ml. acetonitrile, 967 mg. pyrrolidine and 3 gm. cesium carbonate in a reaction flask. Add methylene chloride and wash with water, remove the solvent and excess reactants to recover the title compound.

Prepare the hydrochloride salt by reacting the title compound with 1.1 eq. of 0.1N hydrochloric acid.

EXAMPLE 23

1-[6-(1-imidazolyl)hexyl]imidazole

(a) Heat the reflux for 20 minutes, 5 gms. of 1,6-dibromohexane, 15 ml. acetone and 15.2 gms. sodium iodide. Treat with a water wash in methylene chloride then remove the solvent to recover 1,6-diiodohexane.

(b) Stir overnight at room temperature 1 gm. of the diiodo compound from step (a), 10 ml. DMF and 2.67 gm. sodium imidazole. Treat with methylene chloride and wash with water, dry and remove the solvent to recover the title compound as a crystalline material.

Prepare the hydrochloride by reacting the title compound with about 1 eq. of 0.1N hydrochloric acid.

EXAMPLE 24

Sodium 1-[6-(2-chloro-4-methoxyphenoxy) hexyl]1,4-dihydro-4-oxo-7-methyl -1,8-naphthyridine-3-carboxylate

Stir overnight at room temperature 1 gm. of the iodide prepared in Examples 2 or 3, 10 ml. DMF, 834 mg. 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid and 326 mg. sodium hydroxide in a reaction flask. Wash with water in methylene chloride. Elute on a coarse silica column with methylene chloride then 3% methanol/methylene chloride to isolate the title compound as the carboxylic acid.

Prepare the sodium salt of the title compound by reaction with 0.1N sodium hydroxide.

EXAMPLE 25

1-[6-(2-methyl-1-imidazolyl)hexyl]-2-methylimidazole

Stir overnight at room temperature, 10 ml. DMF, 1.18 gm. sodium hydroxide, 2.43 gm. 2-methyl imidazole and 1 gm. 1,6-diiodohexane in a reaction flask. Treat with methylene chloride and wash with water. Dry on sodium sulfate and remove the solvent to yield the title compound.

Prepare the hydrochloride salt of the title compound by reacting with about 1 eq. of 0.1N hydrochloric acid.

EXAMPLE 26

Mixture of 1-[6-(2-chloro-4-methoxyphenoxy) hexyl]-3-and-5-pyrazole

Stir overnight at room temperature, 1 gm. of the iodide prepared in Examples 2 and 3, 10 ml. DMF, 0.656 ml. (3 eq.) 3-methylpyrazole and 348 mg. sodium hydroxide in a reaction flask. Add methylene chloride and wash several times with water, dry and remove solvent to obtain a mixture of the title compounds.

The title compounds do not form water soluble salts.

EXAMPLE 27

9-[6-(2-chloro-4-methoxyphenoxy)hexyl]purine and 7-[6-(2-chloro-4-methoxyphenoxy)hexyl]purine

Stir overnight at room temperature, 300 mg. of the iodide prepared in Examples 2 and 3, 3 ml. DMF, 147 mg. purine and 49 mg. sodium hydroxide in a reaction flask. Add methylene chloride and wash with water. Elute on a coarse silica column with methylene chloride, then 2% methanol/methylene chloride, then 4 and 5% methanol/methylene chloride to obtain a major amount of the 9-substituted title compound and a minor amount of the 7-substituted title compound.

The title compounds do not form water soluble salts.

EXAMPLE 28

1-[6-(2-chloro-4-methoxyphenoxy)hexyl]-4-methyl-5-hydroxymethylimidazole and 1-[6-(2-chloro-4-methoxyphenoxy)hexyl]-5-methyl-4-hydroxymethylimidazole

Stir for about 9 hours at room temperature 25 ml. DMF, 5 gm. sodium hydroxide, 3.5 gms. 4-hydroxymethylimidazole and 3.0 gms of the iodide prepared in Examples 2 and 3 in a reaction flask. Partition with water/methylene chloride. Elute on a silica column with 100% methylene chloride then 8% methanol in methylene chloride to obtain a mixture of the title compounds. NMR (nuclear magnetic resonance) indicates two isomers are present.

Separate the isomers on a silica column with 50/50 THF/ethylacetate. Recover one isomer as the top spot and the other isomer as the bottom spot.

Prepare the hydrochloride of each title compound by reacting with about 1 eq. of 0.1N hydrochloric acid. MS: m/z 353 (M^+) Both isomers, free base H^1-NMR-200 mHz $^\delta$H ($CDCl_3$), 1.3-1.7 (4H,m), 1.7-2.0 (4H,m), 2.22 (3H, broad s), 3.78 (3H,s) 3.85 (2H,t,J 7Hz), 4.00 (2H,t,J 7Hz), 4.6 (2H,s,5 or 4 -CH_2OH), 4.65,s,4 or 5 -CH_2OH), 6.7-7.0 (3H,m), 7.4 (1H,s)

EXAMPLE 29

1-[6-(2-chloro-4-methoxyphenoxy) hexyl]-2-ethylimidazole

Stir at room temperature for four days 2 gms. of the iodide prepared in Examples 2 or 3, 2 gms. of 2-ethylimidazole, 2.5 ml. DMF and 0.4 gm sodium hydroxide in a reaction flask. Remove the solvent and partition with water/methylene chloride. Elute on a silica column with 100% methylene chloride and then 10% methanol to yield the title compound. MS:m/z 337 (M^+) H^1-NMR-200 mHz, $^\delta$H ($CDCl_3$), 1.34 (3H,t,J 7.5 Hz), 1.3-1.65 (4H,m), 1.70-1.90 (4H,m) 2.66 (2H,q,J 7.5Hz), 3.75 (3H,s), 3.83 (2H,t,J 7Hz), 3.95 (2H,t,J 6Hz), 6.7-7.0 (5H,m).

Prepare the hydrochloride salt by reacting with about 1.1 eq. of 0.1N hydrochloric acid.

EXAMPLE 30

2-[6-(2-chloro-4-methoxyphenoxy)-1-hexylthio]-benzimidazole

Stir at room temperature for four days 2.5 gms. 2-mercapto-benzimidazole, 2 gms. of the iodide prepared in Examples 2 or 3, 25 ml. DMF and 0.71 gm. sodium hydroxide in a reaction flask. Remove the solvent and partition with water/methylene chloride. Elute on a silica column with 100% methylene chloride then 50/50 ethylacetate/methylene chloride to obtain the title compound. MS: m/z 391 (M^+) H^1-NMR-200 mHz-$^\delta$H ($CDCl_3$), 1.5-1.6 (4H,m), 1.7-1.9 (4H,m), 3.35 (2H,t,J 7Hz), 3.75 (3H,s) 3.95 (2H,t,J 6Hz), 6.7-7.0 (3H,m), 7.2-7.4 (4H,m), 7.65-7.75 (1H,m).

EXAMPLE 31

1-[6-(2-chloro-4-methoxyphenoxy)hexyl]-4-methyl-2-ethylimidazole and 1-[6-(2-chloro-4-methoxyphenoxy)-hexyl]-5-methyl-2-ethylimidazole

Stir for four days at room temperature 2 gms of 2-ethyl-4-(5)-methylimidazole, 3 gms. of the iodide prepared in Examples 2 or 3, 0.75 gms. sodium hydroxide and 25 ml. DMF in a reaction flask. Remove the solvent and partition with water/methylene chloride. Elute on a silica column with 100% methylene chloride then 5% methanol to obtain a 70:30 weight ratio of the title compounds as evidenced by NMR of their hydrochloride salts.

Prepare the hydrochloride salts by reaction with 1 eq. of 0.1N HCl.

MS: M/z 351 (M^+) HCl salt, H^1-NMR-200 mHz-$^\delta$H($CDCl_3$), 1.2-1.7 (7H,m), 1.7-2.0 (4H,m), 2.32 (3H,s,isomeric 4-CH_3), 2.40 (3H,s,isomeric 5-CH_3), 3.05 (2H,q,J 8Hz), 3.75 (3H,s), 3.90-4.05 (4H,m), 6.7-7.1 (4Hz).

EXAMPLE 32

1-[3-(2-chloro-4-methoxyphenoxy)propyl]imidiazole

(a) Prepare 1-[3-(2-chloro-4-methoxyphenoxy)propyl]bromide by reacting 10 gm of 2-chloro-4-methoxyphenol, 51 gm of 1,3-dibromopropane, 35 gm K_2CO_3 in 60 ml acetone under reflux for 48 hours. Remove acetone by distillation. Extract residue with methylene chloride and filter. Remove solvent and distill residue under vacuum to recover the product, b.p. 150-160 • C at 0.5 mm Hg.

(b) Stir for 18 hours at room temperature, 1 gm of the bromide prepared in step (a), 2 gms. imidazole, 1.2 gm. sodium hydroxide and 10 ml. DMF in a reaction flask. Remove the solvent and partition with water/methylene chloride to obtain the title compound.

Prepare the hydrochloride salt by reacting the title compound with about 1 eq. of 0.1N HCl. Purify the salt in methylene chloride/water.

FAB-MS: m/z 267 (M^+), HCl salt, H^1-NMR-200 mHz, $^\delta$H ($CDCl_3$), 2.48 (2H,m), 3.76 (3H,s), 4.00 (2H,t,J 5.5 Hz), 4.63 (2H,t,J 6.8 Hz), 6.72-7.00 (3H,m), 7.24 (1H,s), 7.36 (1H,s) 9.68 (1H,s).

EXAMPLE 33

2-[7-(2-chloro-4-methoxyphenoxy) heptyl]-1-methylimidazole

Add 196 mg. 1,2-dimethylimidazole and 5 ml. freshly distilled THF to a dry reaction flask, cool to -78°C then add 0.81 ml. of 2.5 molar n-butyl lithium in hexane, stir 15 minutes at -78°C, then add 0.5 gms of the iodide prepared in Examples 2 and 3 and 5 ml. THF and stir for two hours while slowly warming to room temperature.

Stir the reaction mixture overnight at room temperature. Add 5 ml. water, remove the solvent, then add methylene chloride and wash with water, dry over sodium sulfate then elute on a coarse silica column with methylene chloride then 3% ethanol/methylene chloride to obtain the title compound.

Prepare the hydrochloride salt of the title compound by reacting with about 1.1 eq. of 0.1N hydrochloric acid.

EXAMPLE 34

2-[7-(2-chloro-4-methoxyphenoxy)heptyl]imidazole

(a) Prepare 2-methyl-1-triphenylmethyl-imidazole by refluxing 1.75 gms. 2-methylimidazole, 10 ml. THF and 2 gms. trityl chloride overnight. Recover the product as follows: Add methylene chloride, wash with water, then elute on a coarse silica column with methylene chloride followed by 5% methanol/methylene chloride.

(b) Prepare the title compound as follows: Add 500 mgs. of the compound of step (a) to 10 ml. dry THF then cool to -78°C, add over 3-5 minutes 0.61 ml. n-butyl lithium, then add 376 mg. of the iodide prepared in Examples 2 and 3 in 3 ml. THF over 5 minutes. Stir overnight while slowly warming to room temperature. Remove about 80 to 90% of the solvent, add methylene chloride, wash with water, then brine, and dry over sodium sulfate. Elute on a coarse silica column with methylene chloride, then 10% ethylacetate/methylene chloride, and finally 20% ethylacetate/methylene chloride. Treat the resulting product with 15 ml. formic acid and heat to 100°C for 1.5 hours, let cool to room temperature and a white precipitate forms. Remove the formic acid and neutralize with 10% sodium hydroxide solution to recover the title compound.

Prepare the hydrochloride salt by reacting the title compound with about 1 eq. of 0.1N HCl.

EXAMPLE 35

2-[7-(2-chloro-4-methoxyphenoxy) heptyl]-1-butylimidazole

Stir overnight at room temperature, 79 mgs. of the compound prepared in Example 34, 2 ml. DMF, 29.4 ml. sodium hydroxide and 44.8 mg. n-butyl iodide in a reaction flask. Add methylene chloride and wash with water. Elute on a coarse silica column with 2% methanol/methylene chloride then 3% methanol/methylene chloride and finally 5% methanol/methylene chloride to isolate the title compound.

Prepare the hydrochloride by reacting the title compound with about 1 eq. of 0.1N HCl.

EXAMPLE 36

1-[6-(4-phenoxyphenoxy)hexyl]imidazole

(a-1) Prepare 6-(4-phenoxyphenoxy)hexyl-1-bromide by adding together in a reaction flask at room temperature, 25 ml. DMSO (dimethylsulfoxide), 5 gm. p-phenoxyphenol, 6 gm. of 0.1074 moles potassium hydroxide and 13.1 gm. 1,6-dibromohexane. The reaction is exothermic and a solid results. Add 25 ml. more of DMSO and stir 45 minutes to yield the desired bromide.

(a-2) Add to a reaction flask 10 ml. DMSO, 1.2 gm. powdered KOH, 4.9 ml. 1,6-dibromohexane and 1 gm. solid p-phenoxyphenol. The reaction is exothermic. Add methylene chloride and wash with water. Elute on a coarse silica column with 10% methylene chloride/hexane, then 20% methylene chloride/hexane, the 30% methylene chloride/hexane and finally 40% methylene chloride/hexane to isolate the desired bromide compound.

(b) Heat to reflux for 10 minutes, 1.4 gm. of the compound prepared in step (a-1) or (a-2), 3 gms. sodium iodide and 20 ml. acetone in a reaction flask. Remove the acetone, add methylene chloride, wash with

water then brine and dry over sodium sulfate. Remove the solvent and the desired product, 6-(4-phenoxyphenoxy)-hexyl-1-iodide, crystallizes.

(c) Stir for about 48 hours at room temperature 300 mg. of the iodide from step (b), 5 ml. DMF and 204 mg. sodium imidazole in a reaction flask. Add methylene chloride and wash with water, then brine and dry over sodium sulfate. Dissolve in methylene chloride and filter to obtain the title compound.

Prepare the hydrochloride salt by reaction with about 1.1 eq. of 0.1N HCl.

EXAMPLE 37

Dimethyl 1-[6-(2-chloro-4-methoxyphenoxy) hexyl]-4,5-imidazole dicarboxylate

Stir for 24 hours at room temperature 3.7 gm. dimethyl 4,5-imidazole dicarboxylate, 3.7 gm. of the iodide prepared in Examples 2 or 3, 25 ml. DMF and 2.8 gm potassium carbonate. Remove the solvent, extract the residue with methylene chloride, filter, wash methylene chloride fractions with water, elute on a silica column with 100% methylene chloride then 10% methanol/methylene chloride to recover the title compound.

Free base H^1-NMR-200 mHz, $^{\delta}H$ ($CDCl_3$) 1.3-1.7 (4H,m), 1.7-1.9(4H,m), 3.75 (3H,s), 3.92(6H,s), 3.95 (2H,t,J 8Hz), 6.7-7.0 (3H,m), 7.55 (1H,s)

EXAMPLE 38

1-[6-(2-chloro-4-methoxyphenoxy)hexyl]-4,5-di(hydroxymethyl)imidazole

Add 1 gm. of the compound prepared in Example 37 to 20 ml. THF (dry N_2) cool to 0 • C and slowly add $Li(C_2H_5)_3BH$ and stir for about 30 minutes. Warm to room temperature and stir for about 90 minutes. Add 2 ml. concentrated hydrochloric acid, stir for about 30 minutes and then add sufficient 50% sodium hydroxide to neutralize the acid and obtain a pH of 10-11. Filter to remove the solid. Add 75 ml. THF, 2 ml. 50% NaOH, 3 ml. of 30% hydrogen peroxide and stir for about one hour. Add 30 ml. saturated NaCl solution and 50 ml. methylene chloride. Dry the resulting organic layer with sodium sulfate and evaporate to obtain the title compound.

FAB-MS: m/z 369 (M^+), HCl salt, H^1-NMR-200 mHz, $^{\delta}H$ ($CDCl_3$), 1.3-1.6 (4H,m), 1.6-2.0 (4H,m), 3.72 (3H,s), 3.93 (2H,t,J 6Hz), 4.25 (2H,t,J 8Hz), 4.64 (2H,s), 4.68 (2H,s), 6.7-6.9 (3H,m), 8.95 (1H,s).

EXAMPLE 39

Trans 1-[(2-chloro-4-methoxyphenoxy)methyl]4-[(1-imidazolyl)methyl]cyclohezane

(a) Add 14.5 gm. of trans 1,4-bis hydroxymethyl cyclohexane to 250 ml. methylene chloride and add 20 ml. methanesulfonyl chloride, cool to 0 • C and slowly add 36 ml. triethylamine over a period of one hour. Remove the solvent, extract with water, filter and wash with methanol to obtain trans 1,4-bis mesylate methyl cyclohexane.

(b) Add 30 gms. of the mesylate prepared in step (a) to 300 ml. methylethyl ketone (MEK), then add 90 gm. sodium iodide and reflux for about 30 minutes.

Remove the solvent and extract with methylene chloride to yield trans 1,4-bis iodomethyl cyclohexane.

(c) Add 3 gms. of 2-chloro-4-methoxyphenol, 15 gms. of the diodo compound prepared in step (b), 100 ml. water, 100 ml. methylene chloride in a reaction flask, add 0.5 gm (n-butyl) ammonium sulfate and 25 ml 50% aqeuous NaOH. Elute on a silica column. A mixture of mono and bis ether results as evidenced by NMR.

Add the resulting mixture to 3 gm. sodium imidazole in 20 ml. DMF. Stir at room temperature for about 48 hours. Remove the solvent and elute on a silica column with 100% methylene chloride then 5% methanol to yield the title compound.

Prepare the hydrochloride salt by reaction with 0.1N HCl.

FAB-MS: m/s 335 (M^+) HCl salt, H^1-NMR-200 mHz, $^{\delta}H$ ($CDCl_3$), 0.9-1.30 (4H,m), 1.6-2.1 (6H,m), 3.75 (3H,s), 3.77 (2H,d,J 6Hz), 4.2 (2H,d,J 6Hz), 6.7-7.0 (3H,m), 7.14 (1H,s), 7.43 (1H,s), 9.55 (1H,s).

EXAMPLE 40

1-(9,9-dimethyl-dec-7-ynyl)-imidazole

(a) Add 5 ml. freshly distilled THF and 413 mg. 3,3-dimethyl-1-butyne to a dry reaction flask, cool to -78°C then add 2.01 ml. n-butyl lithium (2.5M in hexane), stir about 30 minutes at -78°C, transfer into 3 ml. THF and 4.9 gm. 1,6-dibromo hexane at 0°C, stir 6 hours and add 2 ml. dry DMSO to form a precipitate. Wash with water, in methylene chloride. Elute through a short bed of silica with hexane to remove polar material giving a mixture of 1,6-dibromo hexane and 1 bromo-(9,9-dimethyl-dec-7-yne.

(b) Stir overnight at room temperature 4.73 gm. of the mixture prepared in step (a), 5 ml. DMF and 2.1 gm. sodium imidazole, in a reaction flask. Add methylene chloride, wash with water, then brine and dry over sodium sulfate. Elute on a coarse silica column with methylene chloride, then 2% methanol/methylene chloride. Combine fractions containing product and chromatograph on a coarse silica column with 25% ethylacetate/methylene chloride, then 35% ethylacetate/methylene chloride to isolate the title compound.

Prepare the hydrochloride salt by reaction with about 1.1 eq. of 0.1N HCl.

EXAMPLE 41

1-[6-(2-chloro-4-methoxyphenoxy)hexyl]-3-methylimidazolium iodide

Stir at room temperature for about 2.5 hours, 300 mg. of the compound prepared in Example 1, 5 ml. methylene chloride and 0.066 ml. methyl iodide. Elute on a coarse silica column with methylene chloride, then 5% methanol/methylene chloride and finally 10% methanol/methylene chloride, to isolate the title compound.

EXAMPLE 42

1-[6-(2-chloro-4-methoxyphenoxy) hexyl]-4 and 5-aminomethyl imidazole

Stir overnight at room temperature, 0.5 gm NaOH, 20 ml. DMF, 4(5) triphenylmethylaminomethyl imidazole and the iodide prepared in Examples 2 and 3, in a reaction flask. Remove the solvent and partition with methylene chloride/water, then brine. Elute on a silica column with 100% methylene chloride, then 40% ethylacetate. Two fractions (the top spot and the bottom spot) containing the trityl protected title compounds separate.

Recover each of the title compounds as follows:

Add the desired fraction to 20 ml. formic acid/2 ml. methylene chloride in a reaction flask and stir overnight at room temperature. Remove all volatiles, partition with 1% HCl H_2O/hexane then add 50% NaOH to a pH over 10. Partition with water/methylene chloride. Elute the methylene chloride residue on a silica column with methylene chloride, then 20% methanol in CH_2Cl_2 to yield the desired title compound. The ratio of the top spot fraction compound to the bottom spot fraction compound is about 4 to 1.

Prepare the hydrochloride salt of each title compound by reaction with about 1 eq. of 0.1N HCl.

(4 or 6 NH_2-CH_2-), free base FAB-MS: m/z 338 (M^+); H^1-NMR-200 mHz, $^\delta$H ($CDCl_3$), 1.3-1.55 (6H,m), 1.60-1.9 (4H,m), 3.75 (3H,s), 3.85 (2H,s), 3.9-4.2 (4H,m), 6.7-7.0 (4H,m), 7.45 (1H,s).

(4 or 5 NH_2-CH_2-), HCl salt FAB-MS: m/z 338(M^+) H^1-NMR-200 mHz, $^\delta$H ($CDCl_3$), 1.3-1.7 (4H,m), 1.7-1.9 (4H,m), 3.75 (3H,s), 3.9-4.0 (4H,m), 4.08 (2H,s), 6.7-7.0 (3H,m), 7.28 (1H,s), 7.52 (1H,s).

EXAMPLE 43

1-[6-(2-chloro-4-methoxyphenoxy)hexyl]-4,5-dimethyl imidazole

(a) Prepare 1-(6-(2-chloro-4-methoxyphenoxy)hexyl]-4(5)-methyl-5(4)-hydroxymethyl imidazole as follows: Add 3gm of 6(2-chloro-4-methoxyphenoxy)hexyl-1-iodide prepared in Example 1, 2.5 gm 4-hydroxymethyl-5-methyl imidazole, 1 gm NaOH to 25 ml DMF (dimethylformamide), stir for 48 hours. Remove DMF by high vacuum, partition with H_2O/CH_2Cl_2, purify methylene chloride residue on silica column with 100% methylene chloride then 10% CH_3OH/CH_2Cl_2 to give the product.

(b) Stir overnight at room temperature the compound prepared in step (a) and 30 ml. thionyl chloride. Heat to reflux for 5 minutes then remove the $SOCl_2$ and chase with toluene.

(c) Add 50 ml. THF to the product prepared in step (b) and cool to 0°C, add 12 ml. (1 eq.) triethyl lithium borohydride and stir for 10 minutes, warm to room temperature and stir for one hour. Add 20 ml. 10% sodium hydroxide then 6 ml. 30% H_2O_2, stir for one hour, add saturated NaCl solution and wash with saturated NaCl solution twice. Dry with sodium sulfate, remove THF and elute on a silica column with methylene chloride, then 2% methanol to obtain the title compound.

Prepare the hydrochloride salt by reaction with about 1 eq. of 0.1N HCl.

FAB-MS: m/z (337M^+) HCl salt H^1-NMR-200 mHz, $^\delta$H($CDCl_3$), 1.35-1.7 (4H,m), 1.7-2.0 (4H,m), 2.22 (3H,s), 2.38 (3H,s), 3.78 (3H,s), 3.98 (2H,t,J 5Hz), 4.15 (2H,t,J JHz), 6.7-7.0 (3H,m), 8.95 (1H,s).

EXAMPLE 44

1-[6-(2-chloro-4-methoxyphenoxy) hexyl]-2-hydroxymethyl imidazole

Add 50 ml. of 37% formaldehyde to 3 gms. of the compound prepared in Example 1, in a Paar bomb and purge with nitrogen. Heat in an oil bath at 130°C for 16 hours. Remove all liquids under vacuum. Partition with 10% sodium hydroxide/methylene chloride then water/methylene chloride. Elute on a silica column with methylene chloride then 8% methanol to obtain the title compound.

Prepare the hydrochloride salt by reaction with about 1 eq. 0.1N HCl.

FAB-MS: m/z 339(M^+ HCl salt, H^1-NMR-200 mHz, $^\delta$H($CDCl_3$), 1.3-1.7 (4H,m), 1.7-2.0 (4H,m), 3.75 (3H,s), 3.96 (2H,t,J 6Hz), 4.24 (2H,t,J 8Hz), 5.02 (2H,s) 6.7-7.0 (3H,m), 7.12 (1H,d,J 2Hz), 7.34 (1H,d,J 2Hz).

EXAMPLE 45

1-allyloxycarbonylmethyl-2-[7-(2-chloro-4-methoxyphenoxy)heptyl]imidazole

Stir overnight at room temperature 4 gms. of the compound produced in Example 34, 20 ml. dry DMF, 545 mg. powdered sodium hydroxide, 2.8 gms. slowly added allyl iodo acetate. Add methylene chloride and wash with water, then brine and dry over sodium sulfate. Elute on a coarse silica column with methylene chloride, then 20% methanol/CH_2Cl_2 and finally with 5% methanol/methylene chloride to isolate the title compound.

Prepare the hydrochloride salt by reaction with about 1 eq. of 0.1N HCl.

EXAMPLE 46

1-carboxymethyl-2-[7-(2-chloro-4-methoxyphenoxy)heptyl]imidazole

Stir for 3 hours at room temperature a mixture of 100 mg. of the compound made in Example 45, 2 ml. THF and 0.2 ml. of 10% NaOH solution. Adjust the pH to about 7.

Add methylene chloride. Remove all water and solvents to obtain a white solid. Add CH_2Cl_2, stir and filter solids. Recover the title compound.

EXAMPLE 47

1-[6-(2-chloro-4-methoxyphenoxy)hex-2-ynyl]imidazole

(a) Add 30 ml. THF and 10 ml. DMSO to a reaction flask and cool to -78°C. Add 7.4 ml. n-butyl lithium (2.5M/hexane), stir for five minutes and add 2.6 gms. of tetrahydropyran protected propargyl alcohol and warm to room temperature. Stir 5 minutes and add 3 gms. of 1-(2-chloro-4-methoxyphenoxy)propyl-3-bromide resulting in a slightly exothermic reaction. Stir for about 1.5 hours. Remove the THF by vacuum and partition with water/methylene chloride. Elute the methylene chloride residue on a silica column with 25% methylene chloride/hexane then 50/50 methylene chloride/hexane. Add the resulting product to 50/25/25 THF/H_2O/CH_3OH and add 1 gm. para toluene sulfonic acid. Stir overnight, remove THF/methanol, partition with 5% $NaHCO_3$/CH_2Cl_2 then with water/methylene chloride. Remove the CH_2Cl_2 to obtain the desired product, 1-hydroxy-6-(2-chloro-4-methoxyphenoxy)hex-2-yne.

(b) Add 25 ml. thionyl chloride to 1.17 gms. of the compound prepared in step (a) and reflux for 1 hour. Remove the thionyl chloride. Add 25 ml. DMF and 3 gms. sodium imidazole and stir overnight. Remove the DMF and partition with H_2O/CH_2Cl_2.

Elute on a silica column with 100% CH_2Cl_2 then 100% ethylacetate to obtain the title compound.

Prepare the hydrochloride salt by reaction with about 1 eq. of 0.1N HCl.

FAB-MS: m/z 305 HCl salt, H^1-NMR, 200 mHz, $^\delta H(CDCl_2)$, 2.05 (2H,m), 2.55 (2H,m), 3.78 (3H,s), 4.08 (2H,t,J 5Hz), 5.20 (2H,m), 6.7-7.0 (3H,m), 7.30 (1H,s), 7.38 (1H,s), 9.6 (1H,s).

EXAMPLE 48

1-acetamido-2-[7-(2-chloro-4-methoxyphenoxy)heptyl]imidazole

Add 100 mg. of the compound prepared in Example 45 and 5 ml. methylene chloride to a reaction flask. Saturate with ammonia gas at room temperature. Let sit for about 30 minutes. TLC with 5% methanol/CH_2Cl_2 indicates a more polar product is in about 50% of the mixture. Stir for about 2 hours, add sodium ethoxide in ethanol, then ammonia and stir for about 1.5 hours. Recover the title compound on TLC.

Prepare the hydrochloride salt by reaction with about 1 eq. of 0.1N HCl.

EXAMPLE 49

1-(2-hydroxyethyl)-2-[7-(2-chloro-4-methoxyphenoxy)heptyl]imidazole

Add 100 mg. of the compound prepared in Example 45, 5 ml. THF and excess lithium aluminum hydride to a reaction flask and stir about 20 minutes. Add ethylacetate, water and ammonium chloride and let sit overnight at room temperature.

Extract with ethylacetate and elute on a coarse silica column with methylene chloride, then 5% methanol/methylene chloride and finally 10% methanol/methylene chloride. The title compound is recovered. Prepare the hydrochloride salt by reaction with about 1 eq. of 0.1N HCl.

EXAMPLE 50

1-(8-phenyl-oct-7-ynyl)imidazole

(a) Prepare 6-phenylethynylhexyl-1-bromide by adding 1.07 ml phenylacetylene to 10 ml of THF in a reaction flask, cool to -78 °C then add 3.9 ml n-BuLi (2.5 molar in hexane), stir 5 minutes, warm to 0 °C and add 45 ml of 1,6-dibromohexane and 5 mol of dry DMSO. Stir at room temperature for 1.5 hours, remove solvent and treat with methylene chloride and water to recover the product.

(b) Stir for 48 hours at room temperature in a reaction flask, 1.65 gms of the products of step (a) and 1.68 gm sodium imidazole in 5 ml DMF. Remover the resulting title compound by treating with methylene chloride, washing with water and drying over sodium sulfate. Then elute on a coarse silica column with 100% methylene chloride followed by 2% CH_3OH/CH_2Cl_2 to yield the title compound.

Prepare the hydrochloride salt by reaction with 0.1N HCl.

MS: m/z 253 (M^+) HCl salt.

EXAMPLE 51

1-[6-hydroxy-6-(2-chloro-4-methylphenyl)hexyl]imidazole

(a) Prepare 6-(2-chloro-4-methoxyphenyl)6-oxo-hexyl-1-bromide by adding 200 ml methylene chloride, 5.87 ml m-chlorotoluene and 11.7 g 6-bromohexanoyl chloride to a reaction flask, then adding 7.95 g aluminum chloride. Stir 3 hours. Wash with water, sodium bicarbonate, water and brine, dry over sodium sulfate then elute on a coarse silica column with 100% hexane, 10% methylene chloride/hexane, 15% methylene chloride/hexane and 20% methylene chloride/hexane to yield the product.

(b) Prepare 1[6-hydroxy-6-(2-chloro-4-methylphenyl)hexylbromide by adding 1 gm of the product of step (a), 10 ml ethanol and 124 mg sodium borohydride. Stir 1 hour at room temperature. Remove the solvent, add methylene chloride, wash with water, brine and dry to recover the product.

(c) Stir for 96 hours in a reaction flask 975 mg of the product of step (b), 10 ml DMF and sodium imidazole. Treat with methylene chloride, wash with water, then brine, dry over sodium sulfate then elute on a coarse silica column with methylene chloride then 3% methanol/methylene chloride to yield the title compound.

Prepare the hydrochloride salt of the title compound by reaction with 0.1N HCl.

FAB MS: m/z 293 (M^+)-HCl salt.

EXAMPLE 52

1-[7-oxy-7-(4-methoxyphenyl)heptyl]imidazole

(a) Prepare 7-(4-methoxyphenyl-7-oxo)heptyl-1-bromide by stirring for one hour at room temperature, 2.16 gm anisole, 100 ml methylene chloride, 7-bromoheptanoyl chloride and aluminum chloride. Wash with water, sodium bicarbonate solution, water then brine. Dry over sodium sulfate. Elute on a coarse silica column with hexane then methylene chloride/hexane to recover the product.
(b) Heat to reflux for 45 mins. 0.5 gm ofthe product of step (a), 10 ml MEK (methylethylketone) and 1.25 gm sodium iodide. Remove most of the MEK, add methylene chloride, then wash with water, followed by brine and dry over sodium sulfate to give the iodide of the compound prepared in step (a). Add 450 mg of sodium imidazole in 10 ml DMF and stir for 48 hours. Add methylene chloride, wash with water, then wash with brine and dry over sodium sulfate to yield the title compound.
Prepare the hydrochloride salt by reaction with 0.1N HCl.
FAB-MS: m/z 287 (M^+)-HCl salt.

EXAMPLE 53

1-[7-hydroxy-7-(4-methoxyphenyl)heptyl]imidazole

Stir at rrom temperature for 2.5 hours, 1 gm of the compound prepared in Example 52(b), 10 ml ethanoland 0.5 gm sodium borohydride. Remove most of the ethanol, add methylene chloride and wash with water, elute on a coarse silica column with methylene chloride then 3% methanol/methylene chloride to obtain the title compound.
MS: m/z 288 (M^+)-base.

EXAMPLE 54

1-[7-(4-methoxyphenyl)-hept-6-enyl]-imidazole hydrochloride

Treat the compound prepared in Example 53 with 1.1 eq. of 0.1N HCl to give the title compound.
FAB/Gly-Thio-MS: m/z 271 (M^+) HCl salt.

EXAMPLE 55

1-[7-hydroxyimino-7-(4-methoxyphenyl)heptyl] imidazole

Stir overnight at room temperature 0.5 gm of the compound prepared in Example 52(b), 10 ml ethanol, 1 ml water and a large excess of hydroxyl amine·HCl and stir for 4 hours. Remove most of the ethanol by bubbling nitrogen through the reaction mixture. Adjust the pH to about 10 with 10% aqueous NaOH, add methylene chloride and wash with water, then brine and dry over sodium sulfate. Then elute on a coarse silica column with methylene chloride then 1, 2, 3 and 4% methanol/methylene chloride to give the title compound.
Prepare the hydrochloride salt by reaction with 1.1 eq. of 0.1N HCl.
MS: m/z 302 (M^+) HCl salt.

EXAMPLE 56

1-[7-(4-methoxyphenyl)heptyl]imidazole

Shake overnight under 30 psi hydrogen pressure, 87 mg of the free base of the compound prepared in Example 54, 20 ml anhydrous ethanol and PtO. Filter and remove the ethanol then elute on a coarse silica column with methylene chloride then 2% methanol/methylene chloride to obtain the title compound.
Prepare the hydrochloride salt by reaction with 1.1 eq. of 0.1N HCl.
MS: m/z 272 (M^+) HCl salt.

EXAMPLE 57

1-[7-oxo-7-(4-methylthiophenyl)heptyl]imidazole

(a) Prepare 7-(4-methylthiophenyl-7-oxo)-heptyl-1-bromide by stirring for 2.5 hours, 2.34 ml thioanisole, 5 gm 7-bromoheptanoylchloride and 3.19 aluminum chloride in 100 ml methylene chloride at room temperature. Slowly add water then wash with water, sodium bicarbonate solution, water and brine. Elute ona coarse silica column with 40% methylene chloride/hexane then 50% methylene chloride/hexane to give the product as white crystals.
(b) Add 100 ml acetone and 6.5 gm sodium iodide to the product of step (a) and heat to reflux for 1.5 hours, remove the solvent. Treat with methylene chloride and wash with water to obtain the iodide of the compound produced in step (a).
(c) Add 30 ml of DMF to the compound produced in step (b), add sodium imidazole and stir overnight. Treat with methylene chloride and wash with water, then elute on a coarse silica column with methylene chloride then 3% methanol/methylene chloride to yield the title compound.
Make the hydrochloride salt by reaction with 0.1N HCl.
FAB/Gly-Thio-MS: m/z 303 (M^+)HCl salt.

EXAMPLE 58

1-[7-hydroxyimino-7-(4-methylthiophenyl)heptyl imidazole

Stir for 5 hours at room temperature 300 mg of the compound produced in Example 57(c), 10 ml ethanol, 1 ml water and 344 mg hydroxylamine·HCl. Bubble nitrogen through the reaction mixture to remove the ethanol, add methylene chloride and wash with 10% sodium hydroxide, water, then brine to yield the title compound.
Prepare the hydrochloride salt by reaction with 0.1N hydrochloric acid.
FAB/Gly-Thio-MS: m/z 318 (M^+) HCl salt.

EXAMPLE 59

1-[7-hydroxy-7-(4-methylthiophenyl)heptyl]imidazole

Stir at room temperature for 2 hours, 200 mg of the compound prepared in Example 57, 5 ml ethanol and 50 mg sodium borohydride. Remove the ethanol with nitrogen, add methylene chloride then wash with water then brine and dry over sodium sulfate to obtain the title compound.
Make the hydrochloride salt by reaction with 1.2 eq. of 0.1N HCl.
FAB/Gly-Thio-MS: m/z 305 (M^+) HCl salt.

EXAMPLE 60

1-[7-oxo-7-(4-methylsulfonylphenyl)heptyl] imidazole

To 1 gm of the compound prepared in Example 57 and 20 ml acetic acid slowly add over one hour 6 ml 30% hydrogen peroxide and let stand at room temperature for 3.5 hours.
Add 10% sodium hydroxide in methylene chloride, wash with water, then brine and remove the solvent to obtain the title compound.
FAB/Gly-Thio-MS: m/z 335 (M^+) HCl salt.

EXAMPLE 61

1-[7-methoxyimino-7-(4-methylsulfonylphenyl)heptyl]imidazole

Stir for 4.5 hours at room temperature, 100 mg of the compound produced in Example 60, 5 ml ethanol, 0.5 ml water and 125 mg methoxyamine hydrochloride. Remove most of the ethanol with nitrogen, add methylene chloride and 10% sodium hydroxide. Wash with water, then brine and dry over sodium sulfate to obtain the title compound.
Prepare the hydrochloride salt by reaction with 1.1 eq. of 0.1N HCl.

FAB/Gly-Thio-MS: m/z 364 (M^+) HCl salt.

EXAMPLE 62

1-[7-hydroxyimino-7-(4-methylsulfonylphenyl)heptyl]imidazole

Stir for 5 hours at room temperature 130 mg of the compound prepared in Example 60, 5 ml ethanol, 0.5 ml water and 135 mg hydroxylamine hydrochloride. Remove the ethanol with nitrogen, add methylene chloride, 10% sodium hydroxide, wash with water then brine and dry over sodium sulfate to obtain the title compound.

Prepare the hydrochloride salt by reaction with 1.1 eq. of 0.1N HCl.

FAB/Gly-Thio-MS: m/z 350 (M^+) HCl salt.

EXAMPLE 63

1-[7-hydroxy-7-(4-methylsulfonylphenyl)heptyl]imidazole

Stir for 3 hours at room temperature, 150 mg of the compound prepared in Example 60, 5 ml ethanol and 34 mg sodium borohydride. Remove the solvent (ethanol) with nitrogen. Add water and methylene chloride and partition. Wash with water then brine and dry over sodium sulfate to recover the title compound.

Prepare the hydrochloride salt by reaction with 1.05 eq. of 0.1N HCl.

FAB/Gly-Thio-MS: m/z 337 (M^+) HCl salt.

EXAMPLE 64

N-[6-(1-imidazolyl)hexanoyl]-1-adamantanamine

(a) Stir for 0.5 hours at 0 °C in a reaction flask, 9.5 gm adamantanamine and 12 gm 6-bromohexanoyl chloride in 200 ml THF. Remove the THF and partition with methylene chloride/water then methylene chloride/5% HCl, then methylene chloride/5% sodium carbonate and finally methylene chloride/water to yield 6-(1-adamantanamine)-6-oxohexyl-1-bromide.

(b) Add 1 gm of the compound produced in Example 64(a) and 2 gms sodium imidazole to 25 ml DMF, stir overnight at room temperature. Remove the solvent under vacuum. Partition with 100% methylene chloride then 5% methanol/methylene chloride to yield the title compound.

Prepare the hydrochloride salt by reaction with 0.1N HCl.

EXAMPLE 65

1-[6-(5-chloro-2-methoxy-4-methylphenyl) hexyl]imidazole and 1-[6-(3-chloro-6-methoxy-2-methylphenyl)-hexyl]imidazole

(a) Add 1 gm of 2-chloro-5-methoxytoluene to 50 ml THF, cool to about -8 °C then add 4.5 ml of n-butyl lithium 2.5M in hexane, allow to warm to about 10 °C then add to a cool solution of 10 gm of 1,6-dibromohexane and 2.25 gms potassium teritary butoxide in 50 ml THF. Stir for 0.5 hr. then warm to room temperature. Stir overnight, cool and remove the solvent. Partition with water/methylene chloride to yield 1-[6-(5-chloro-2-methoxy-4-methylphenyl)hexyl]bromide mixed with 1-[6-(3-chloro-6-methoxy-2-methylphenyl)hexyl]bromide, boiling point 120-140 °C at 0.05 mm Hg.

(b) Add 1.7 gm of the mixture prepared in step (a) to 3 gms sodium imidazole in 25 ml DMF and stir overnight. Remove the solvent and partition with water/methylene chloride. Elute on a silica column with 100% methylene chloride then 10% methanol to give a mixture of the title compounds which are separated by HPLC chromatography.

Prepare the hydrochloride salts of the title compounds by reaction with 1.1 eq. of 0.1N HCl.

EXAMPLE 66

1-[6-oxy-6-(4-methoxyphenyl)hexyl]imidazole

(a) Add 1.1 gm anisole to 2.2 gm 1-bromohexanoyl chloride in 100 ml methylene chloride. Add 1.5 gm aluminum chloride and stir for 45 mins. Partition with water, 5% $NaHCO_3$ and water. Remove solvent and recover 1-[6-oxy-6-(4-methoxyphenyl)hexyl]bromide.
(b) Stir for 48 hours at room temperature 2.6 gms of the compound produced in step (a) and sodium imidazole (4 eq.) in 25 ml DMF. Partition with water/methylene chloride. Remove the solvent. Elute on a silica column with 100% methylene chloride then 5% methanol to obtain the title compound.
Prepare the hydrochloride salt by reaction with 0.1N HCl.

EXAMPLE 67

1-[6-oxy-6-(2,4-dimethoxyphenyl)hexyl]imidazole

(a) Add 1.4 gm 2,4-dimethoxybenzene and 2.2 gm 1-bromohexanoyl chloride to 100 ml methylene chloride. Add 1.3 ml tin chloride and stir for 0.5 hr. Wash with water then 5% sodium bicarbonate to yield 1-[6-oxy-6-(2,4-dimethoxyphenyl)hexyl]bromide.
(b) Add 2.8 gm sodium imidazole in DMF to 3 gm of the compound produced in step (a). Stir for 48 hours, remove DMF, partitition with water/methylene chloride, elute on silica column with 100% methylene chloride then 5% methanol/methylene chloride to yield the title compound.
Prepare the hydrochloride salt by reaction with 0.1N HCl.

EXAMPLE 68

1-[6-hydroxy-6-(2,4-dimethoxyphenyl)hexyl]imidazole

Add 50 ml of ethanol to 1.3 gm of the compound prepared in Example 67, then add 0.5 gm sodium borohydride. Stir for 2.5 hours, remove the solvent, extract with methylene chloride, elute on a silica column with 100% methylene chloride, then 5% methanol/methylene chloride to yield the title compound.

EXAMPLE 69

1-[6-(2,4-dimethoxyphenyl)hex-5-enyl]imidazole, hydrochloride

Treat 0.266 gm of the compound prepared in Example 68 with 11 ml of 0.1N HCl to give the title compound.

EXAMPLE 70

1-[6-oxy-6-(2-chloro-4-methoxyphenyl)hexyl]imidazole

(a) Add 2.85 gm of meta-chloroanisole to 4.5 gm 1-bromo-hexazoyl chloride in 200 ml methylene chloride. Add 3.2 gm aluminum chloride and stir for 2.5 hours. Add water and stir overnight. Partition with water/methylene chloride, then 5% sodium bicarbonate/methylene chloride. Elute on a silica column with hexane, then methylene chloride to yield 1-[6-oxy-6-(2-chloro-4-methoxyphenyl)hexyl]bromide.
(b) Add 1.5 gms of the compound prepared in step (a) to sodium imidázole prepared from 2.8 gms imidazole and 0.8 mg sodium hydroxide in 25 ml DMF and stir overnight. Remove the solvent then partition with methylene chloride/water. Elute on a silica column with 100% CH_2Cl_2 then 5% methanol/methylene chloride to yield the title compound and as a side product pentyl, para, meta, chloroanisole ketone.
Prepare the hydrochloride salt by reaction with 0.1N HCl.

EXAMPLE 71

1-[6-hydroxy-6-(4-methoxyphenyl)hexyl]imidazole

Add to 1 gm of the title compound prepared in Example 66 in 50 ml ethanol, 0.5 gm sodium borohydride, stir for 2.5 hours then remove the solvent. Extract with methylene chloride. Elute on a silica column with 100% methylene chloride then 5% methanol/methylene chloride to yield the title compound.

EXAMPLE 72

1-[6-(4-methoxyphenyl)hex-5-enyl]imidazole, hydrochloride

Add 0.529 gms of the compound prepared in Example 71 to 22 ml 0.1N HCl to yield the title compound.

EXAMPLE 73

1-[6-hydroxy-6-(2-chloro-4-methoxyphenyl)hexyl]imidazole

Add 25 ml ethanol to 300 mg of the title compound prepared in Example 70, then add 400 mg sodium borohydride, stir for 2 hours. Remove the solvent. Partition with water/methylene chloride. Elute the methylene chloride residue on a silica column with 100% methylene chloride then 5% methanol/methylene chloride to yield the title compound.

EXAMPLE 74

1-[6-(4-methoxyphenyl)hexyl]imidazole

Add 1 ml water to 400 mg of the compound prepared in Example 72, then add 100 mg sodium bicarbonate followed by 25 ml ethanol. Add 100 mg PtO and add hydrogen under 30 psi for 20 hr. Partition with water/methylene chloride. Elute on a silica column with 100% methylene chloride then 5% methanol/methylene chloride to yield the title compound.

Prepare the hydrochloride salt by reaction with 0.1N HCl.

EXAMPLE 75

1-[6-(naphthalene-2-oxy)hexyl]imidazole

(a) Add 5 gm of beta-naphthol to 100 ml methylene chloride then add 27 ml 1,6-dibromohexane followed by 0.5 gm tetra n-butyl ammonium sulfate then 75 ml water and 25 ml of 50% sodium hydroxide. Stir for 48 hours, partition with water/methylene chloride, remove the methylene chloride and distill the residue at 0.1 mm mercury to give the product 1-[6-(naphthalene-2-oxy)hexyl]bromide.

(b) Add 2 gm of the compound produced in step (a) to a solution of 2 gm imidazole and 0.5 gm sodium hydroxide in 20 ml DMF and stir overnight. Remove the solvent, partition with methylene chloride/water. Elute on a silica column with 100% methylene chloride then 5% methanol to yield the title compound.

Prepare the hydrochloride salt by reaction with 0.1N HCl.

EXAMPLE 76

1-[6-(4-methylthiophenoxy)hexyl]imidazole

(a) Add 10 gm 4-methylthiophenol and 1,6-dibromohexane to 200 ml methylene chloride, and 150 ml water, then 2 gm tetra n-butyl ammonium sulfate and 50 ml of 50% NaOH solution. Stir overnight, wash with water then brine, remove methylene chloride and distill off excess dibromohexane at 70 °C and 0.1 mm mercury in a 90 °C temperature bath. Crystallize the resulting compound, 1-[6-(4-methylthiophenoxy)hexyl]bromide, from hexane.

(b) Dissolve 1.5 gm sodium hydroxide and 5 gm imidazole in DMF. Add 5 gm of the compound prepared in step (a) and stir 48 hours. Remove the solvent, partition with water/methylene chloride. Elute on a

silica column with 100% methylene chloride then 5% methanol to obtain the title compound.

Prepare the hydrochloride salt by reaction with 0.1N hydrochloric acid.

EXAMPLE 77

1-[6-(4-methylsulfonylphenoxy)hexyl]imidazole

Add 1 gm of the title compound prepared in Example 76 to 50 ml acetic acid. Then add 6 ml of 30% hydrogen peroxide. Stir for 3 hours. Add 6 ml more of 30% hydrogen peroxide and stir overnight. Add sufficient 15% sodium hydroxide to adjust the pH to 11. Partition with methylene chloride/water. Remove methylene chloride and recover the title compound.

Prepare the hydrochloride salt by reaction with 0.1N hydrochloric acid.

EXAMPLE 78

1-[6-(4-methoxyphenylthio)hexyl]imidazole

(a) Add to a reaction flask 10 gm p-mercaptoanisole, 55 ml 1,6-dibromohexane, 150 ml water, 200 ml methylene chloride, 50 ml of 50% sodium hydroxide and finally 2 gm tetra n-butylammonium sulfate and stir overnight. Partition with water/methylene chloride then brine/methylene chloride. Remove excess dibromohexane. Add the resulting residue to hexane, remove crystalline disulfide side product then remove the hexane to obtain 1-[6-(4-methoxyphenylthio)hexyl]bromide.

(b) Dissolve 5 gm imidazole and 1.5 gm sodium hydroxide in DMF. Add 5 gms of the compound prepared in step (a) and stir overnight. Remove the solvent, partition with water/methylene chloride. Elute the methylene chloride. Elute the methylene chloride fraction on a silica column with 100% methylene chloride then with 5% methanol/methylene chloride to yield the title compound.

Prepare the hydrochloride salt by reaction with 0.1N hydrochloric acid.

EXAMPLE 79

1-[6-(4-methoxyphenylsulfonyl)hexyl]imidazole

Add 3.5 gm of the title compound prepared in Example 78 to 125 ml acetic acid, then add 24 ml of 30% hydrogen peroxide in 2 portions, 24 hours apart, stir for 48 hours. Adjust pH to >10 with 25% sodium hydroxide. Partition with water/methylene chloride. Elute on a silica column using 100% methylene chloride then 5% methanol to yield the title compound.

Prepare the hydrochloride salt by reaction with 0.1N hydrochloric acid.

Claims

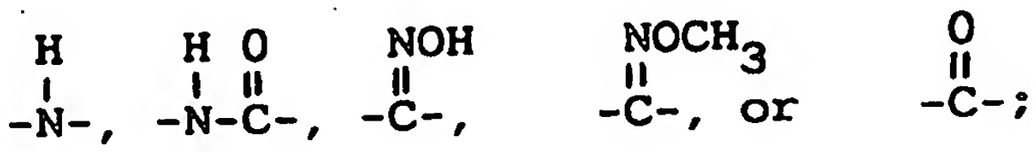
1. A compound respresented by formula II

Z-X-Q-Y-W'-Y-Q-X-Z II

and pharmaceutically acceptable acid addition, basic addition and quarternary amine salts thereof and pharmaceutically acceptable solvates thereof, wherein

each Z independently is tertiary butyl, phenyl, naphthyl or adamantyl; substituted phenyl, wherein the substituents are one or more of halogen, C_1-C_{10} alkoxy, phenoxy, nitrile, nitro, phenylsulfonyl. C_1-C_{10} alkyl-sulfonyl, oxazol-2-yl, C_1-C_{10} alkanoyl, benzoyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkyl, C_1-C_{10} alkylthio, phenyl, phenylaminothiocarbonyl, or C_1-C_{10} alkylaminothiocarbonyl; 4 to 6 membered unsubstituted or substituted heterocyclic ring containing at least one nitrogen with the remaining members of the ring being at least one carbon, and optionally sulfur or oxygen, wherein the substituents are one or more of carboxyl, hydroxymethyl, C_1-C_{10} alkyl, C_1-C_{10} alkylcarbonyl, phenyl C_1-C_{10} alkyl or naphthyl C_1-C_{10} alkyl;

X and Y are each independently a bond, -O-, -S-, -SO_2-,



each Q is independently a divalent substituted or unsubstituted, straight or branched chain C_1-C_{10} alkanediyl, C_1-C_{10} alkanediyl-C_4-C_7 cycloalkanediyl-C_1-C_{10} alkanediyl, C_2-C_{10}alkenediyl, C_2-C_{10} alkynediyl, phenylene, dihydrofurandiyl, tetrahydrofurandiyl, tetrahydropyrandiyl or, C_1-C_{10} alkanediyltetrahydrofuranediyl-C_1-C_{10} alkanediyl, wherein the substituents are one or more of hydroxy, epoxy, fluorine, chlorine, azide, or amino;

W' is a divalent substituted or unsubstitued phenyl or naphthyl group or a heterocyclic single or fused ring containing from 4 to 10 ring atoms, at least one hetero atom of which is a nitrogen atom and the remaining ring atoms being at least one carbon and optionally sulfur or oxygen, wherein the substituents are one or more of hydroxy, oxo, amino, carbamoyl, carboxyl, nitrile, nitro, C_1-C_{10} alkoxy carbonyl, fluorine, chlorine, iodine, sulfamyl, C_1-C_{10} alkyl, C_1-C_{10} alkylthio, C_1-C_{10} alkoxy, hydroxy C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl C_1-C_{10} alkyl, amino C_1-C_{10} alkyl, carboxy C_1-C_{10} alkyl, guanidino, thioureido, C_1-C_{10} alkylsulfonyl-amino, aminocarbonyl C_1-C_{10} alkyl, allyloxycarbonylmethyl or carbamoyloxy C_1-C_{10} alkyl; with the proviso that W cannot be substituted or unsubstituted isoxazolyl.

2. A compound as claimed in Claim 1 in which each Z is bonded to each X by a nitrogen or carbon atom, and W' has two nitrogens each of which is bonded to a separate -Y-Q-X-Z moeity.

3. A compound as claimed in Claim 1 or 2 in which Z is substituted or unsubstituted phenyl, with substituents as previously described.

4. A compound as claimed in any of Claims 1-3 in which W' is a divalent substituted or unsubstituted heterocyclic single ring with 6 ring atoms, with substituents as previously described.

5. A compound as claimed in any previous claim selected from:
1,3-di[6-(2-chloro-4-methoxyphenoxy)hexyl]-1,2,3,4-tetrahydropyrimidine-2,4-dione; and N,N'-bis-[6-(2-chloro-4-methoxyphenoxy)hexyl]-2-benzimidazolone.

6. A compound as claimed in any previous claim for use as an active therapeutic substance.

Claims for the following Contracting States : GR, ES

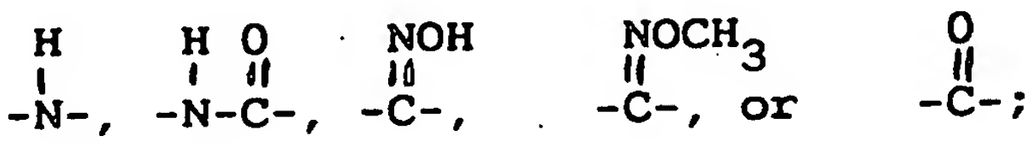
1. A process for producing a compound represented by formula II

Z-X-Q-Y-W'-Y-Q-X-Z II

and pharmaceutically acceptable acid addition, basic addition and quarternary amine salts thereof and pharmaceutically acceptable solvates thereof, wherein

each Z is independently tertiary butyl, phenyl, naphthyl or adamantyl; substituted phenyl, wherein the substituents are one or more of halogen, C_1-C_{10} alkoxy, phenoxy, nitrile, nitro, phenylsulfonyl, C_1-C_{10} alkyl-sulfonyl, oxazol-2-yl, C_1-C_{10} alkanoyl, benzoyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkyl, C_1-C_{10} alkylthio, phenyl, phenylaminothiocarbonyl, or C_1-C_{10} alkylaminothiocarbonyl; 4 to 6 membered unsubstituted or substituted heterocyclic ring containing at least one nitrogen with the remaining members of the ring being at least one carbon, and optionally sulfur or oxygen, wherein the substituents are one or more of carboxyl, hydroxymethyl, C_1-C_{10} alkyl, C_1-C_{10} alkylcarbonyl, phenyl C_1-C_{10} alkyl or naphthyl C_1-C_{10} alkyl;

X and Y are each independently a bond, -O-, -S-, -SO_2-,



each Q is independently a divalent substituted or unsubstituted, straight or branched chain C_1-C_{10} alkanediyl, C_1-C_{10} alkanediyl-C_4-C_7 cycloalkanediyl-C_1-C_{10}-alkanediyl, C_2-C_{10} alkynediyl, phenylene, dihydrofurandiyl, tetrahydrofurandiyl, tetrahydropyrandiyl or, C_1-C_{10} alkanediyltetrahydrofuranediyl-C_1-C_{10} alkanediyl, wherein the substituents are one or more of hydroxy, epoxy, fluorine, chlorine, azide, or amino;

W' is a divalent substituted or unsubstitued phenyl or naphthyl group or a heterocyclic single or fused ring containing from 4 to 10 ring atoms, at least one hetero atom of which is a nitrogen atom and the remaining ring atoms being at least one carbon and optionally sulfur or oxygen, wherein the substituents are one or more of hydroxy, oxo, amino, carbamoyl, carboxyl, nitrile, nitro, C_1-C_{10} alkoxy carbonyl, fluorine, chlorine, iodine, sulfamyl, C_1-C_{10} alkyl, C_1-C_{10} alkylthio, C_1-C_{10} alkoxy, hydroxy C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl C_1-C_{10} alkyl, amino C_1-C_{10} alkyl, carboxy C_1-C_{10} alkyl, guanidino, thioureido, C_1-C_{10} alkylsulfonyl-amino, aminocarbonyl C_1-C_{10} alkyl, allyloxycarbonylmethyl or carbamoyloxy C_1-C_{10} alkyl; with the proviso that W cannot be substituted or unsubstituted isoxazolyl, characterised by

(A), reacting compounds of the formula

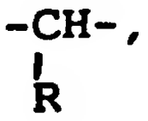
$$Z\text{-}X\text{-}Q'\text{-}L^1$$

with a compound of the formula

$$L^3\text{-}Y'\text{-}W'''\text{-}Y'\text{-}L^4$$

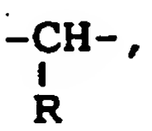
wherein Z and X are as defined previously,
Q' is the same as Q defined previously, or, provided Q is to contain at least one of the groups

wherein each R is independently hydrogen or C_1-C_{10}alkyl, Q' may also be the same as Q defined previously minus at least one of the groups



L^1 is a leaving group,
Y' is the same as Y defined previously, or, provided Q is to contain at least one of the groups

wherein each R is independently hydrogen or C_1-C_{10}alkyl, Y' may also be the same as Y defined previously plus at least one of the groups



L^3 and L^4 are leaving groups,
W''' is divalent W' as defined above;
wherein any reactive groups are protected if necessary or desired;
the above process followed if necessary or desired by
(i) removal of any protecting groups,

(ii) conversion of a compound so produced to another compound of formula II,
(iii) if more than one compound of formula II is produced, separation of the compounds so produced, or
(iv) conversion of any of the compounds so produced to an acid addition, basic addition, or quaternary amine salt or pharmaceutically acceptable solvate thereof.

2. A process as claimed in Claim 1 for producing: 1,3-di[6-(2-chloro-4-methoxyphenoxy)hexyl]-1,2,3,4-tetrahydropyrimidine-2,4-dione; and N,N'-bis-[6-(2-chloro-4-methoxyphenoxy)hexyl]-2-benzimidazolone.

3. The use of a compound of formula II as defined in Claim 1 or 2 in the manufacture of a medicament.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 93 10 7518.8

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	EP-A-0 086 043 (PFIZER) * the whole document * ---	1,6	C07D233/60 C07D277/36 C07D257/04
A	US-A-4 540 703 (MINORI UCHIDA ET AL.) * the whole document * ---	1,6	C07D213/70 C07D249/08 C07D239/54
A	EP-A-0 049 060 (BEECHAM) * the whole document * ---	1,6	C07D233/64 C07D235/26 C07D233/91
A	US-A-3 190 888 (MILTON WOLF ET AL.) * the whole document * ---	1,6	C07D213/30 C07D413/12 C07D235/06
A	EP-A-0 112 292 (CIBA-GEIGY) * the whole document * ---	1	C07D473/00 C07D233/90 A61K31/41
A	EP-A-0 218 543 (SANDOZ) * the whole document * ---	1	
A	EP-A-0 210 753 (YAMANOUCHI) * the whole document * ---	1,6	
A	EP-A-0 051 827 (A.NATTERMAN) * the whole document * -----	1,5,6	TECHNICAL FIELDS SEARCHED (Int. Cl.4) C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	08 JULY 1993	FRANCOIS J.C.

EPO FORM 1503 03.82 (P0401)

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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